EFFECT OF RADIOTHERAPY FOR BREAST CANCER ON TOTAL AND REGIONAL LUNG FUNCTION

By

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DECLARATION

I hereby declare that the work for this thesis was carried out solely by me. This thesis has not been submitted for any other degree.

Amal I.M. Kanbour

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ABSTRACT

When modern high voltage radiotherapy is used in combination with simple mastectomy for the treatment of breast cancer, the lung apex on the treated side receives up to 4250 rads. Minor changes in overall lung function following such therapy have previously been reported (Emirgil and Heinemann, 1961). These changes are more pronounced when radiation pneumonitis develops, which occurs in about 11% of such patients (Gross, 1977).

Two groups of patients were studied, both having had simple mastectomy followed by megavoltage radiotherapy (4250 rads to the axilla and supraclavicular region and 4500 rads to the chest wall by tangential fields, in 10 fractions over four weeks), as part of their treatment for carcinoma of the breast.

Overall and regional lung function measurements, chest x-ray and electrocardiograph were carried out in each patient. Overall lung function was assessed by static lung volumes (TLC, VC, RV, RV/TLC%), dynamic lung volumes (FEV_1, FVC, FEV_1/FVC%), transfer factor of carbon monoxide (T_{CO}), flow volume curves and airways resistance. Regional distribution of ventilation was measured with radioactive Xe^{133}, and regional distribution of perfusion with radioactive Xe^{133} in the first study and with Tc^{99m} macro-aggregated albumin in the second study, using a gamma camera linked on-line to a computer.

The first study involved a longitudinal sequential measurement in the same group of ten patients prior to radiotherapy, but after simple mastectomy "control" and at 1, 3, 6, 9 and 12 months after radiotherapy. There were no signficant changes in VC, FVC, T_{CO}, $\dot{V}_{max}$ 50, $\dot{V}_{max}$ 30 and

sGaw after radiotherapy, as compared to control values. However, there was a significant reduction at 5% level in TLC, RV and FEV_1 at 6, 9 and 12 months after radiotherapy, as compared to the control values. Chest x-rays were unchanged in most of these patients. Comparison of regional ventilation between the irradiated and the non-irradiated "control" lung at the same vertical height showed no changes either before radiotherapy or sequentially at 1, 3, 6, 9 and 12 months thereafter. However, there was a significant reduction in perfusion of the upper zones of the irradiated lung corresponding to the region receiving the radiotherapy in most of these patients. This perfusion reduction was significant at the 5% level at 1 month and at 6 months after radiotherapy, but was not significant thereafter.

The second study was a cross-sectional one in a group of 48 patients at an interval of one to fourteen years after radiotherapy, given by the same technique. The chest x-rays showed some changes in 52% of these patients. Their values of TLC, VC and FEV_1 were distributed around 100% of the predicted normal values, thus showing normal values, but their T_{CO} was below 100% of the predicted normal value in most. There was no significant change in regional ventilation between the irradiated and the non-irradiated lungs, when compared at the same vertical height, but there was a highly significant reduction in perfusion of the upper zones of the irradiated lung, as compared to the non-irradiated "control" lung in the same patient.

It is concluded that:

1) This dose and technique of radiotherapy had little effect on overall lung function in these women with normal lungs.

2) However, perfusion to the alveolus was reduced in the irradiated region, without clinical or radiological changes, from as little as one month, to as long as 14 years after radiotherapy in some patients.

3) The earliest effect of radiotherapy appears to be upon the pulmonary vascular bed in the irradiated region.

ABBREVIATIONS

Post RT	Post radiotherapy
Hb	Haemoglobin
WBC	White blood cell
ECG	Electrocardiograph
CXR	Chest x-ray
TLC	Total lung capacity (litres)
VC	Vital capacity (litres)
RV	Residual volume (litres)
FEV_1	Forced expiratory volume at 1.0 second (litres)
FVC	Forced vital capacity (litres)
$\dot{V}_{max}$ 50	Maximum flow at 50% VC (litres/sec)
$\dot{V}_{max}$ 30	Maximum flow at 30% VC (litres/sec)
T_{CO}	Transfer factor for carbon monoxide (mmol/min/kPa)
sGaw	Specific airway conductance ($sec.^{-1}kPa^{-1}$)
Irr	Irradiated
Non-Irr	Non-irradiated
Diff	Difference
V	Volume
$\dot{V}$	Volume per unit of time in the gas phase
$\dot{Q}$	Volume per unit of time in the blood phase
	(Ellis, 1971)
V%	Lung volume% of total lung volume
$\dot{V}/E\%$	Ventilation/alveolus of that if it was uniformly distributed
$\dot{Q}/E\%$	Perfusion/alveolus of that if it was uniformly distributed
E	Regional equilibration count rates at TLC

I. INTRODUCTION

The lung has been defined by Ali B.R. Al-Tabari in 850 A.D. in his book "Paradise of Wisdom" - as "An elastic organ with wide tubes and it happened like that in order to make it easy for the air to enter during inspiration, to take out the burden from the heart during contraction and relaxation".

He also mentions that "any injury in the lungs will heal quickly, but if it is infected, it will dry the chest dampness and push these fluids and secretions through the throat out to the mouth".

On the other hand, cancer has been known even before that time and Hippocrates, who said that "cancer is an untreatable disease and any attempt to treat the cancerous patient will cause death of that patient earlier than if it is left alone". Furthermore, Al-Tabari explained that "cauterizing or burning the cancer will cause its spread to the vital organs and will kill the patient. Unless the cancer is situated peripherally then it could be amputated without causing a great harm to the patient" (Siddiqi, 1928). Thus, it would appear that there is good historical precedence for the idea that the treatment of cancerous patients should be based on the principle of destruction of cancer tissue, either by amputation or by cauterization and burning. Nowadays, possibly following similar principles, cancer is treated by surgery and/or radiotherapy.

i) History of radiotherapy

Following the discovery of x-rays by Roentgen in 1895, Emil H. Grubble used these rays to treat an ulcerated carcinoma of the breast. Moreover, several workers used the rays on many diseases. Also, the Curies discovery of radium added a further source of radiation and this was used at the beginning of the twentieth century for the treatment of tumours lying deep in the body where the electrically generated x-ray penetrated poorly.

Thereafter with developments in technology, more powerful x-rays were produced, operating above 200,000 volts (i.e. Ortho voltage x-ray machines). These machines produced x-rays capable of giving high radiation doses to tissues lying deep in the body using multiple fields all directed at the tumour (Deeley, 1976). To obtain the maximum destructive effect, the maximum dose of radiation to the treatment area was given. Consequently, the effect of overdose, necrosis of tissue, infection and sometimes death occurred. These effects were recognised early and attempts were made to reduce them; for example, the effect of radiation on the lung as a result of radiation therapy to the breast cancer was recognised as early as 1923 by Groover, Christie and Merritt, for the x-ray fields in the treatment of breast cancer then, were applied directly to the breast, therefore inevitably irradiating the underlying lung. Thus the technique of tangential therapy to the chest wall following mastectomy was developed to minimize the effect of radiotherapy on the lung.

Thereafter attempts were made to measure the dose of radiation given to the tumour, so as to provide an adequate dose of radiation to the tumour and yet minimizing that given to normal tissue. A unit of dose was defined as the "roentgen" (R) which is the radiation absorption dose in air (Deeley, 1976). A few years later, with the advancement in medical engineering, new machines were constructed capable of producing high voltage x-rays in the million volt ranges (Mega voltage), e.g. linear accelerator, which produce x-rays at very high energies with enormous penetration. The first linear accelerator used clinically in 1953 worked at 8,000,000 volts (Deeley, 1976).

Mega voltage therapy provided greater penetration of rays in tissue, with a lower skin dose and thus less radiation damage to skin and bones, reduced morbidity and allowed for greater accuracy in definition of treatment fields (Morrison, 1967).

At the same time advances in radiobiology revealed that tumours which are well oxygenated were more sensitive to irradiation that anoxic tumours, leading to the use of hyperbaric oxygen as an adjunct to treatment. Also a better understanding of the effect of radiation on growing tissue was achieved by growing human tumours in culture media.

Later, the development of computers made possible easier and more accurate calculation of the isodose distribution. Progress was made in the location of tumours, ensuring correct alignment of fields using shells and check radiographs. Moreover, a new unit, the rad,

(radiation absorption dose) was used clinically for measuring the dose of radiation in tissue (1 rad = 100 ergs/gm). Careful attention was taken to reduce the radiation effect on normal tissue and attempts were made to increase the effect on the tumour by using mega voltage therapy and the application of radiobiology in addition to the use of computer to calculate isodose distribution and to record clinical details. Clinical trials investigating the value of combined methods of treatment, with surgery, radiotherapy and chemotherapy were undertaken.

ii) Radiation physics

Ionization radiations are those radiations which are capable of interacting with atoms and molecules in the body to produce biological effects. The atom consists of two parts:

1. Nucleus : containing protons with positive charge and neutron with mass only
2. Shells : consisting of an equal number of electrons to the protons, with a negative charge, circulating around the nucleus and maintained in their orbit by the attractive forces of the protons

Some atoms are unstable (e.g. radium) and break down naturally into more stable substances. These unstable atoms all have high atomic weight and during the process of decay, alpha, beta and gamma rays are given off from the atom. Alpha rays are particles which have the total mass of helium nucleus. They can penetrate only a little into the tissue

before they collide with the nucleus of an atom and release their energy. Beta rays are electrons with a smaller mass and penetrate more deeply before losing their energy. Gamma rays are ionizing electro-magnetic radiations with energy, but no mass and thus they are able to penetrate deeply into the tissues. The depth of penetration depends on the energy of such rays, which in turn depends on the atoms whose breakdown or decay leads to the formation of the ray. X-rays, on the other hand, are ionizing electro-magnetic rays with energy, but they are produced electrically.

Thus, x-rays and gamma rays are both electro-magnetic rays, having a wave formation with a wave length and frequency. As an ionizing radiation the x-rays and gamma rays have the smaller wave length than ultra violet in the spectrum of electro-magnetic waves. The energy of x-rays varies according to the energy applied to the machine used to produce them. Essentially they are produced when a stream of electrons, accelerated by a high voltage applied between the cathode and anode, strikes the target (anode) and the electrons give up their energy to produce x-rays with a high energy. A method has been devised for accelerating the passage of electrons down an evacuated tube and thus they hit the target with a very high velocity and produce x-rays at very high energy (e.g. linear accelerator) (Deeley, 1976).

These rays penetrate the tissue and the depth of penetration varies inversely with their wave length; the shorter the wave length, "hard rays", the deeper the

penetration and visa versa. The quality of a radiation beam may be expressed as the "thickness of the absorber which reduces the intensity of radiation by one half" ("half value layer of the beam [HVL]") (Deeley, 1976). In tissues the energy of the radiation beam is absorbed and released locally, the remaining energy at a particular point depending on the distance that it has penetrated and the density of the tissues. Thus, it was possible to measure the energy of a beam at different points in the tissues and a chart joining together points with the same percentage of the dose; these lines being called isodose curves. The dose of any particular point and the shape of the isodose curve varies according to the energy of the radiation beam, e.g. the isodose curve of the linear accelerator is shown in Figure 1.

Measurements of radiation are made in Roentgen, which is the ionization produced in 1 ml of air at normal temperature and pressure (NTP). The measurement of radiation absorbed dose in tissue was introduced (rad), 1 rad being equivalent to 100 ergs/gm of tissue. The units, roentgen and rad, are equals in cases of gamma rays or x-rays.

iii) <u>The uses of radiotherapy</u>

Radiotherapy is used mainly in the treatment of malignant diseases, either alone or in combination with surgery and/or chemotherapy. The selection of the method for treatment may vary with the characteristics of the tumour, site, nature and spread. For example, in breast

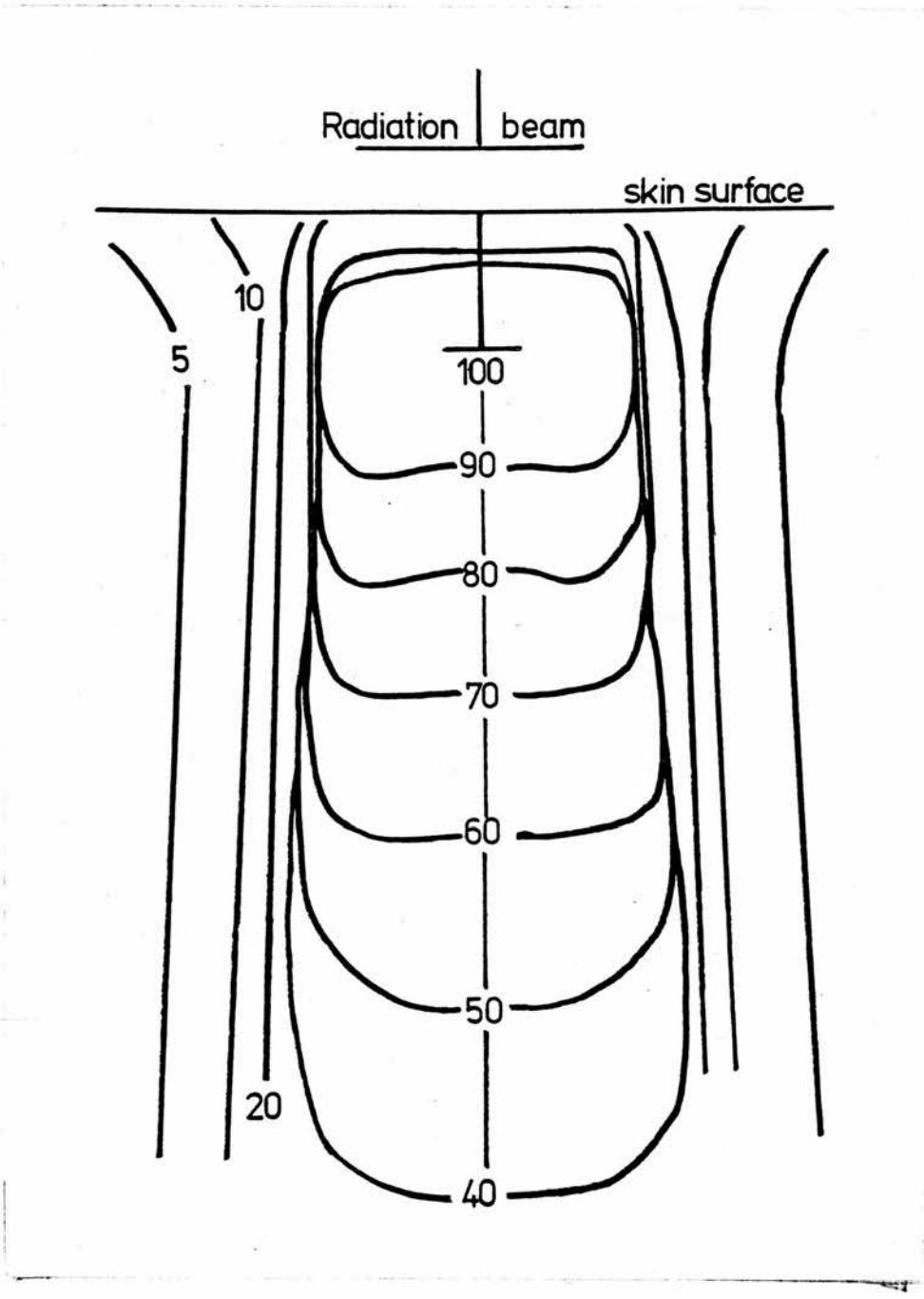


Figure 1

The isodose curve of the linear accelerator. These numbers are the percentage of the dose of the applied radiation beam as distributed below the skin surface. (After Deeley, 1976).

cancer the primary may be removed by surgery and the lymph node area may be treated by radiation.

The radiation treatment given may be radical, aiming at a cure, or palliative, aiming at the control of the disease, e.g. tumours of the breast may be kept in control by the doses of radiation, supplemented by hormones and chemotherapy. On the other hand, radiotherapy may be palliative to relieve distressing symptoms.

In general, the following principles are usually followed in radiation treatment planning (Johns, 1961):

1. A homogenous dose is given to the tumour and the maximum and minimum tumour dose usually evaluated and recorded.

2. The field size selected to just cover the tumour and a safe margin around it and enough number of fields used to make the tumour dose at least 50% larger than any other tissue dose.

3. For ortho and mega voltage radiotherapy the dose at the maximum in skin is usually stated.

4. Correction of the tumour dose for air cavities and surface irregularity is made using bolus (material which has the same radiation absorption characteristics as normal soft tissues). Wedge filters may be used also to correct for irregularities of contour, e.g. in tangential fields in breast.

5. The relative biological effect is determined by the way the dose is administered. Thus the overall treatment time, the number of treatments and the number of fields treated per day are recorded. It is generally accepted that the biological effect of a given amount of radiation depends on the fractionation of the total dose over a period of from 3 to 5 weeks. Accordingly, the overall period between the first and last treatment and the number of exposures is usually stated.

6. The source to skin distance and the half value layer (HVL) or energy of radiation is recorded, as these factors are involved in determining the tumour dose.

iv) The effect of radiation on biological tissues

Radiation leads to ion production along the track of ionizing particles, due to interaction of electro-magnetic radiation with matter. These ions either affect the DNA of the cell directly or indirectly by the interaction of the ions with water, thus generating free radicles (such as H, OH, O, HO2 and H2O2) which are short-lived and very reactive with effects on subsequent cell division and produce chemical changes. After this damage the cell recovers for about 4 hours, then shows the original effect, as revealed by sensitivity to the second dose of radiation. Thereafter further recovery occurs and recovery is maximal at 24 hours after radiation, but still not complete (Ellis, 1967).

Some of the chemical changes produced by the free radicle are reversible, but if oxygen molecules are present, a chemical reaction will take place between the oxygen and the free radicle, producing organic peroxides which cause the chemical lesion in a non-reversible form.

The radiation causes damage both to the genetic material, DNA and non-genetic macromolecules such as proteins and polysaccharides. It causes breakage of polymer strands which can be repaired to some extent in vivo in the first few hours after irradiation. The lethality of damage to genetic material is a function of the mitotic rate of the irradiated tissue.

The damage to the non-genetic material is more immediate and widespread, but probably less lethal. The increased membrane permeability and fragmentation of connective tissue produces immediate effects on function and late effects may also occur by destruction of basement membrane cells, as in the lungs, where this may prevent reconstruction of tissue architecture and result in scar formation and later functional derangement (Gross, 1977).

Bloomer and Hellman (1975) categorised the responses of the normal tissue to radiation therapy as acute, intermediate and late. These responses depend upon such factors as the nature of the irradiated normal tissue, the volume of normal tissue irradiated and the various time-dose features in the treatment programme.

I. Acute effects are more a function of dose rate and time-dose fractionation characteristics than of the total applied dose; they result primarily from the depletion of actively proliferating cells in otherwise homeostatic cell renewal systems. Normal tissues typically involved in these acute radiation reactions are bone marrow, gut, skin and other epithelial tissues.

II. Intermediate effects are related to time-dose fractionation characteristics, as well as total effective dose, and probably result from injury to cells with slowly proliferating renewal systems, as in endothelium or connective tissue. Radiation pneumonitis and pericarditis are important intermediate effects.

III. Late effects are directly related to the total dose received by the limiting normal tissue within a treatment portal. This is assumed to be endothelium or connective tissue (Rubin and Casarett, 1968). It involves a slowly proliferating endothelial cell renewal system, or causes alteration of the structural integrity of certain macromolecules in the connective tissue stroma (Bloomer et al, 1975).

v) Effect of radiation on the lungs

The term radiation pneumonitis was given to early changes in the lung following radiation, whereas the term radiation fibrosis was given to the late changes.

The clinical recognition of the intra-thoracic changes following radiotherapy of malignant disease (breast carcinoma) was first reported by Groover, Christie and Merritt in 1923. These authors described the first case of lung reaction and compared this reaction to skin changes. Subsequently there have been many reports concerning the occurrence, clinical features, pathology, radiological and physiological effects of radiation in the lungs.

1. Occurrence

The incidence of radiation pneumonitis was first reported by Evans and Leucutia in 1925. Out of 42 patients treated by deep Roentgen therapy for the mammary carcinoma, 5 patients showed radiographic evidence of pulmonary fibrosis and of these, only one was symptomatic. This paper gave about 12% incidence of radiation pneumonitis. On the other hand, McIntosh and Spitz

in 1939 reported that 60% of their series (i.e. 36/60 patients with breast cancer treated with fractionated radiation treatments of 800-2000 rads to each 5 portals) developed radiographic evidence of pneumonitis at 3 and 6 months after irradiation and 17% became symptomatic (i.e. 10/60 patients).

However, Engelstad in 1940 observed that out of 386 cases of breast carcinoma treated with roentgen (given as a tangential irradiation) and/or radium (given as a tele-radium treatment), only 21 patients developed the radiation reaction in the lung (as detected by radiological changes), i.e. the incidence was 5.4%; whereas Leach, Farrow, Foote and WaWro in 1942 reported 77 instances of roentgenographic evidence of pulmonary fibrosis in 347 patients with breast cancer (i.e. 22.1%). On the other hand, Ross in 1956 used serial radiographs to follow 49 patients with breast cancer who were treated with the "glancing" or tangential technique. The "fibrotic" reaction was slight in 23 patients and more pronounced in 21 patients; only 5 patients showed no evidence of pulmonary changes (i.e. the incidence was about 90%).

Thus the incidence, as shown by radiological changes, varied from 5.4% to 90% in these reports. Differences in technique, awareness, method of reporting and the evolution of radiotherapy itself may account for some of these variations (Gross, 1977).

Considering only breast cancer patients who were treated with mega voltage therapy, the occurrence of radiological changes corresponding to radiation pneumonitis was reported

by Chu, Phillips, Nickson and McPhee (1955) as 24.5% out of 49 patients treated with a tangential technique at 1000 kv roentgen rays. Symptomatic radiation pneumonitis occurred in 8% of these patients. On the other hand, in a series of 50 patients with breast carcinoma, treated on 2 million volt unit, the tumour dose was 3000-5000 given in 5 weeks. Bate and Guttman (1957) found that 35 patients (i.e. 70%) developed radiation pneumonitis, detected radiologically within 6 months after radiotherapy. Only 7 patients (i.e. 14%) had subjective respiratory complaints attributed to radiation. Late radiological changes corresponding to radiation fibrosis occurred in 30 patients of this series (i.e. 60%). They also observed that these changes increased with increasing tumour dose.

In 1959 Gish, Coates, Dusault and Doub reported that 20% of their series developed radiological changes following Cobalt-60 therapy for patients with breast carcinoma. However, Fleming, Filbee and Wiernick in 1961 recorded the incidence of radiation pneumonitis in 135 patients with breast cancer treated with mastectomy (usually radical), followed by a course of radical x-irradiation given in 15 treatments over 35 days, delivered at 250 kv (kilo volt). Radiological changes developed in 56% and symptoms were present in 13% of all patients. Late radiological changes (i.e. fibrosis) was reported in 57%. Thus the mean occurrence of radiation pneumonitis following mega voltage radiotherapy is about 41% (adjusting for the number in each series) and adjusted mean occurrence for symptomatic

radiation pneumonitis is approximately 11% (Gross, 1977).

Radiation pneumonitis is also described in association with treatment of carcinoma of the lung (Hellman, Kligerman, Essen and Scibetta, 1964) and Hodgkin's disease (Libshitz and Banner, 1974).

2. Clinical features

The clinical syndrome can be divided into two consecutive phases (Smith, 1963; Rubin and Casarett, 1968; Gross, 1977):

I. An acute phase called "radiation pneumonitis" (consisting of early x-ray changes and/or symptoms) occurring one to six months after the completion of four to six week course of x-irradiation.

II. A late phase "radiation fibrosis" which may follow the acute phase.

Acute phase

The symptoms in this phase are dependent upon the degree of pulmonary involvement and may vary from none, through vague symptoms of malaise, to severe respiratory distress at rest. If less than half of one lung is involved, there may be mild fever, vague respiratory symptoms and a feeling of "fullness" in the chest. If more lung tissue is involved in the reaction, shortness of breath and cough, particularly on exertion, may appear (Rubin and Casarett, 1968). The cough is an early troublesome symptom which is irritative or harsh and initially non-productive, but, later, small amounts of sputum may be produced. Dyspnoea may be at first present only on exertion, but in a severe case it may progress rapidly to dyspnoea at rest. Fever may appear in

severe cases. Chest pain is rarely a prominent feature, but may be due to associated complications with the radiation pneumonitis, such as rib fracture, pleural or pericardial changes (Gross, 1977). Physical signs in the chest are usually absent, but some times consolidation is present in the region corresponding to pneumonitis. A pleural friction rub or pleural fluid may be detected and skin changes caused by irradiation may provide a clue to the presence or severity of the pulmonary reaction. In severe forms, the pneumonitis can be considered part of the spectrum of the adult respiratory distress syndrome, with cyanosis refractory to oxygen, breathlessness, stiff lungs and widespread alveolar infiltrates on chest x-ray. Occasionally evidence of acute cor pulmonale appears.

The acute stage of clinical radiation pneumonitis may persist for as little as a week and then subside gradually. In severe cases, the progression from mild dyspnoea to death in respiratory failure may occur in a matter of days (Gross, 1977).

Late phase

Symptoms are again directly related to the degree and extent of lung damage. Scarring of up to half of one lung is well tolerated and rarely causes symptoms. Although the majority of patients with clinical radiation pneumonitis may become asymptomatic during later months, nearly all will eventually develop radiological evidence of pulmonary fibrosis in the region of the pneumonitis (Bates and Gutman,

1957; Fleming et al, 1961; Hellman et al, 1964). In few patients (e.g. those who had severe pneumonitis) the distortion of pulmonary architecture by superimposed fibrosis may result in severe physiologic abnormalities and chronic respiratory failure with symptoms of dyspnoea on effort, reduced exercise tolerance, orthopnoea, cyanosis and some times chronic cor pulmonale (Rubin and Casarett, 1968).

The time course of these late changes is variable. Symptoms of pneumonitis (mentioned before) may proceed directly to those of fibrosis (i.e. dyspnoea on effort, orthopnoea and cyanosis) and may be separated from them by an interval of several months, during which scarring becomes more severe. Some patients may present with symptoms only in the state of fibrosis, following a silent pneumonitis. Once a scar develops, it persists for life (Gross, 1977). Occasionally symptoms due to tumour are confused, especially when the radiotherapy has been used to treat lung cancer.

3. Associated complications

a. Pleural changes: Pleural reactions, such as a friction rub or pleural fluid, have been reported by Chu et al (1955) in two out of 18 patients with breast cancer treated with a tangential technique at 250 kv. On the other hand, Bate and Gutman (1957) noted pleural effusions in 3/30 patients treated for breast cancer with a dose of $\leq$5000 rads and in 4/20 patients who received >5000 rads. Moreover, Bachman and Macken in 1959 reported a pleural reaction in 11/200 patients who received radiation therapy for breast cancer. In this series the pleural effusion appeared 2-6 months after

completion of radiotherapy, always accompanied radiation pneumonitis and some times persisting for very long periods.

b. Spontaneous pneumothorax: Libshitz and Banner (1974) reported the occurrence of spontaneous pneumothorax in two patients who received extended field radiation therapy to the thorax for Hodgkin's disease; radiation changes in the lung (i.e. radiation pneumonitis) was present in both patients.

c. Radiation effect on the heart and pericardium: Electrocardiographic (ECG) changes caused by irradiation were reported by Eggers in 1941 who described T-wave changes following x-ray therapy for lung tumours. Thereafter several reports have described the ECG changes following radiation therapy in breast cancer. Catteral and Ogilvie (1959) found that 5/6 patients who had their 250 kv x-ray therapy to the left chest showed ECG changes four months after irradiation; whereas none of the 6 patients who received the same radiation to the right chest developed any ECG changes. The ECG changes consisted mostly of T-wave changes (i.e. flattened, biphasic or inverted T). These findings were confirmed by Catteral in 1960 who noticed abnormal T-waves in the ECG in 9/12 patients with left breast cancer, subjected to post-mastectomy treatment from 250 kv machines. There were no ECG changes in 8 patients with right sided breast cancer. These ECG changes were found also following radiotherapy of malignant intra-thoracic tumours (Jones and Wedgewood, 1960; Takaoka, Kaneda, Urano and Kikkawa, 1968; Rubin and Casarett, 1968). However, the origin or

exact causes of these changes have not been definitely proved. Structual changes in the human myocardium and damage to the normal pericardium have been observed and associated with very large doses of radiation (Rubin and Casarett, 1968). Later on, Westerhof and Vander Putte (1976) reported a case of constrictive pericarditis due to radiation for Hodgkin's disease. At necropsy an extensive fibrosis of the myocardium was located in the anterior part of the heart. On the other hand, Green and Ricks (1977) reported the development of pericardial effusion in 3 patients treated with radiation for carcinoma of the left breast. The effusions were loculated on the right side of the pericardium.

4. Pathological changes in radiation pneumonitis and fibrosis

The lung damage induced by radiation results in a loss of reproductive capacity of dividing cells. Thus the radiation-induced chromosomal changes will be most marked in the bronchial epithelial cells, capillary endothelial cells and type 2 pneumocytes as these cell types have the highest mitotic rates (Spencer and Shorter, 1962; Tannock and Hayashi, 1972; Gross, 1977). The pathological changes of radiation damage have been derived mainly from animal studies, as the pathologic material is irregularly available from humans who have received radiation to the lung and usually these patients show a late stage of radiation damage.

Animal studies

Radiation-induced lung damage was studied by Engelstad (1940) in rabbits. Thereafter several ultrastructural studies

were made in rats (Jenning and Arden, 1961; Phillips, 1966; Adamson, Bowden and Wyatt, 1970; Phillips and Margolis, 1972); and in hamsters (Madrazo, Suzuki and Churg, 1973) and were reviewed by Rubin and Casarett (1968) and Gross (1977).

In general the pathological changes are divided into three chronological phases; the early phase, occurring up to about two months after irradiation, is followed by the intermediate phase from 2-9 months and the late phase after 9 months (text Table 1). Radiation thus has acute damaging effects on all tissues in the lungs. Rubin and Casarett (1968) suggested that the damage and response of the fine vasculature (capillaries, arterioles and venules) and the connective tissue elements played a prime role in the reaction of lung to irradiation. Many authors concluded that damage of capillaries may be the major factor in the genesis of subsequent pathology.

Histopathological changes in humans

Studying the sequence of pathological changes in human radiation pneumonitis is difficult because of the lack of material obtained systematically and also due to the presence of secondary changes resulting from superimposed infection, heart failure and post mortem artefacts. Histological studies on the lungs of patients dying 4-12 weeks after completion of radiation therapy showed lesions in all the structures of the lung.

1. Vascular lesions were evidence by engorgement and thrombosis of capillaries and arterioles, oedema, intimal

TEXT TABLE 1

HISTOPATHOLOGICAL ABNORMALITIES AFTER IRRADIATION OF THE THORAX IN ANIMALS
(After Gross, 1977)

Site	Immediate & Early Changes (0-2 months)	Intermediate (2-9 months)	Late (9+ months)
Capillaries	Increased capillary permeability, endothelial cell changes and separation from basement membrane, sloughing and obstruction of the lumen. Later, many capillaries swollen and obstructed.	Marked capillary abnormalities with widespread obstruction due to platelets fibrin and collagen. Regeneration of capillaries. Reduced capillary permeability.	Loss of many capillaries, regeneration of new capillaries. Reduced capillary peremability.
Type I pneumocytes	Degenerative changes. Or normal.	Decreased number.	Further decreased in number.
Type 2 pneumocytes	Very early degenerative changes, becoming marked with time. Or normal.	Large increase in size and number. Abnormal appearance.	Return to normal size and number.
Basement membrane	Early swelling, indistinct. Later very irregular.	Folded and thickened.	Folded and thickened.
Interstitial space	Oedema and debris, infiltrated with inflammatory cells. Slight increase in connective tissue.	Infiltrated with mononuclear cells, mast cells, inflammatory cells and connective tissue.	Few inflammatory cells. Large increase in collagen.
Alveolar space	Fibrin, haemorrhages and debris. Increased number of alveolar macrophages.	Becomes smaller.	Small or absent. Distortion of architecture.
Bronchial epithelium	Early transient inflammatory reaction, ciliary paralysis, increased goblet cells. Or normal.	Epithelial proliferation.	-

proliferation and medial changes, together with subintimal accumulation of lipid-laden macrophages (Bennett, Million and Ackeaman, 1969; Rubin and Casarett, 1968; Gross, 1977).

2. The alveolar epithelial cells (type 2 pneumocytes) showed atypia, hyperplasia and desquamation (Warren and Spencer, 1940; Jenning and Arden, 1962; Bennett et al, 1969).

3. The alveolar space The presence of fibrin-rich deposition and hyaline membranes in the alveolar space were reported by many authors.

4. The alveolar septum showed early thickening due to oedema, mononuclear cellular infiltration and laying down of connective tissue (Warren and Spencer, 1940; Jenning and Arden, 1962; Bennett et al, 1969).

5. Changes in the bronchial wall, including focal necrosis, of the mucosa have been reported (McIntosh and Spitz, 1939). Pleural changes are occasionally observed (Chu et al, 1955) and changes in the right ventricle have been considered secondary to the pulmonary changes (Smith, 1963).

5. Radiological changes

The earliest radiological evidence of damage occurs at 2-3 months and consists of a ground glass opacification, or diffuse haze (Bate and Gutman, 1957), or indistinctness of the normal pulmonary markings. Depending on the time and severity of the changes, the appearances may be alveolar, nodular or dense, resembling consolidation

(Gross, 1977). Pleural interlobar or pericardial effusions are occasionally noted (Rubin and Casarett, 1968). Hagen and Kolbenstvedt (1971) studied the chest x-ray in 70 patients with breast cancer treated by radical mastectomy followed by irradiation; 13% of these patients had no changes on the x-ray, 23% had slight changes, 43% had moderate changes and 21% had marked changes. The initial changes, influenced by the technique of radiotherapy, appeared at about 2 months as an indefinite, fan-shaped infiltration with its apex pointing towards the hilum; this subsequently changed to radiating strands suggesting fibrosis. Shrinkage gradually followed which caused elevation of the hilum and upper diaphragm. Compensatory emphysema of the lower part of the lung has been observed as well. Pleural thickening was a common change also (Hagen and Kolbenstvedt, 1971).

In general, radiologic pneumonitis will invariably proceed gradually to the stage of radiologic fibrosis unless treated (Libshitz and Banner, 1973). When fibrosis occurs, the lesion shows linear streaks radiating from the area of previous pneumonitis. Contraction of the region, pleural thickening and tenting of the diaphragm are also seen. In severe unilateral cases, contraction of volume may result in retraction of the hilum or mediastinum toward the region, with tracheal deviation, elevation of the diaphragm and the appearance of a densely fibrotic contracted lung segment with compensatory emphysema of the adjacent or contralateral lung tissues (Gross, 1977).

These changes may take 12 months or more to produce and may appear up to 2 years after irradiation (Fleming et al, 1961).

6. Causes of lung damage

The incidence and severity of radiation damage to the lungs are related to several technical factors, including the volume of lung tissue irradiated, the quality of radiation, the total dose and mainly the rate at which the total dose is delivered [as repair of sublethal damage occurs between each fractional dose (Gross, 1977)]. The relationship between the biological effect of radiation [Nominal Standard Dose (NSD) in ret (radequivalent therapy)] and the total dose absorbed (rad), number of fractions (N) and the time over which the total dose is delivered (T) can be described by:

$$NSD\ (ret) = total\ dose\ (rad).\ N^{-0.24}\ .T^{-0.11}$$ (Ellis, 1969

Phillips and Margolis (1972) and Wara, Phillips, Margolis and Smith (1973) have modified this formula to calculate the effect of radiation given to the entire lung volume, in both mice and humans. They found that there is a 50% probability of developing clinical pneumonitis with a dose of 713 ret, or 3050 rad given in 20 fractions over 4 weeks when this dose is given to the entire lungs.

Factors such as concommitant chemotherapy (e.g. bleomycin and radiotherapy), previous radiation therapy or steroid withdrawal have been considered to potentiate the

damaging effects of radiation (Wara et al, 1973; Whitfield, Bond and Arnott, 1956; Castellino, Glatstein, Turbow, Rosenberg and Kaplan, 1974). Age, on the other hand, was not considered as an important contributing factor for the development of radiation damage in the lung (Rubin and Casarett, 1968), but is possibly related to the severity of radiation reaction once it occurs (Hagen and Kolbestvedt, 1972).

7. The physiological changes

Many studies of changes in pulmonary function have been carried out on animals, as well as in human patients with breast or lung cancers. The majority of these studies had radiological changes of radiation pneumonitis and/or radiation fibrosis, and the results differ slightly between these studies. Previous human retrospective studies (Leach et al, 1942, 1943; Whitfield et al, 1956; Stones, Schwartz and Green, 1956) suggested that radiation damage of the lung (radiation fibrosis) causes reduction in lung volumes and maximum breathing capacity as compared to their expected values, based on the usual prediction formulae. Later, several studies of pulmonary function before and after radiation were reported, and comparisons between the results of each measurement were made. Measurements of pulmonary function in animals before and after radiation were made by Sweany, Moss and Haddy (1959) who studied the effect of two different irradiation schedules, applied to the mid-chest of eight dogs (in a single exposure) and of

another seven dogs (in fractionated doses). They found that the functional residual capacity (FRC) (as determined by the open circuit method during spontaneous breathing), total thorax, lung and chest wall compliance (obtained by the static method), the diffusing capacity (estimated by the steady state CO method during spontaneous breathing) and pulmonary vascular resistance (as measured at cardiac catheterisation) were unchanged within the first few weeks following irradiation, although pathologic changes were evident. However, the FRC, lung compliance and pulmonary diffusion capacity then fell progressively at 81, 137 and 172 days following irradiation, but the pulmonary vascular resistance remained normal for a period of five months following irradiation.

Moreover, Teates in 1965 studied the effect of unilateral thoracic irradiation (in fractionated doses) on the lung function in 5 dogs. He compared the function of each lung (i.e. the irradiated and the shielded) prior to irradiation and at frequent intervals up to 207 days after irradiation. The function of the irradiated lung was reduced as compared to the non-irradiated lung in all indices measured (minute ventilation, diffusing capacity, 0_2 consumption and $C0_2$ production and compliance) as shown in Figure 2. This reduction was significant at 200 days after irradiation. The chest x-rays and pathology of the irradiated lung confirmed radiation pneumonitis, although there were considerable variations in the degree of damage from one animal to another and within the same lung.

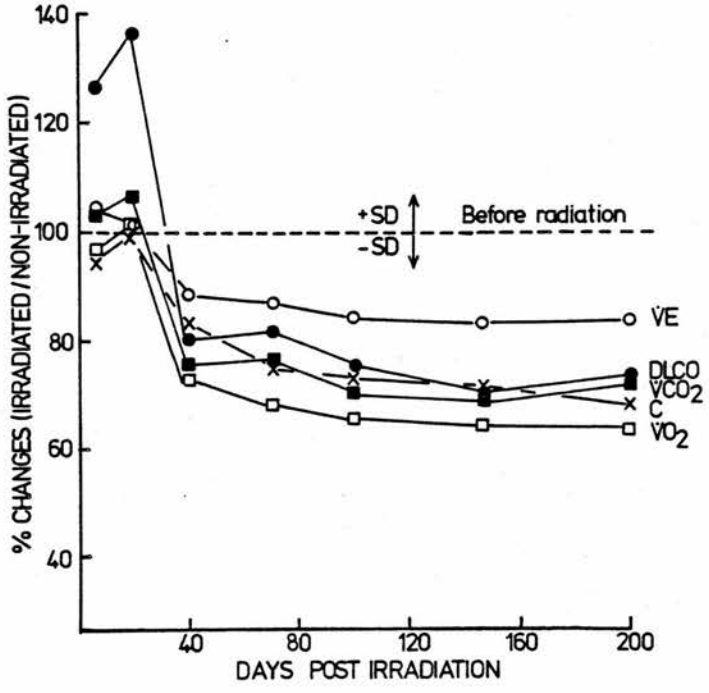


Figure 2

The percentage changes of the ratio (irradiated lung to non-irradiated lung) of ventilation ($\dot{V}_E$), transfer factor for Co (DLCo), compliance (C), oxygen consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$), plotted against time (days) after radiotherapy, in 5 dogs. (After Teates, 1965).

Furthermore, clinical experience has been related to serial physiological studies carried out before and after thoracic irradiation for lung or breast cancer. Catteral and Ogilvie (1959) studied the pulmonary function of 12 patients with breast cancer treated with mastectomy and deep x-ray therapy. They measured the vital capacity, maximum voluntary ventilation and flow rate, the diffusing capacity and an exercise tolerance test before radiotherapy and at two weeks, one month, three months and four months after radiotherapy. They found that there was a reduction in the vital capacity and diffusing capacity four months after radiotherapy. These findings were confirmed by Cooper, Guerrant, Harden and Teates (1961) who found that the ventilatory function (as measured by vital capacity and maximum breathing capacity) was impaired in patients having radiotherapy at 3000-4500 rads tissue dose at 3-5 cms, over 3-5 weeks for their breast cancer. This impairment persisted or progressed as the acute reaction in the lung subsided into the chronic stage (shown by serial x-rays and clinical examination); for example, the vital capacity was reduced by an average of 500 ml at 3 months after irradiation and this reduction persisted at six, nine and 12 month measurements, whereas the arterial oxygen saturation was reduced only in the acute period.

These studies illustrated the importance of studying patients with normal lungs prior to irradiation. Thus, Emirgil and Heinemann (1961) followed 15 patients who were free of cardiac and pulmonary diseases before receiving irradiation so as to determine the effect of radiation on

pulmonary function. Control measurements had been made before irradiation in only four patients with mammary carcinoma (treated with 4000-5000 rads using a 2 MeV machine), in whom serial studies were made during the follow-up period which lasted as long as 297 days after the start of radiotherapy. Their results were as follows:

1. Lung volumes

A measurable reduction in total lung capacity (TLC) was detected from one to three weeks after irradiation in all subjects with unilateral pneumonitis, and this reduction was accompanied by a decrease in vital capacity (VC) and residual volume (RV) (Figure 3).

2. Oxygen and carbon dioxide content and tension in arterial blood

All subjects with unilateral pneumonitis had mild to moderate hypoxia at rest which improved as time elapsed.

3. Diffusing capacity for carbon monoxide and oxygen

Evidence of a transient reduction in diffusion capacity of carbon monoxide (DLCO) appeared later at 60-162 days in patients with unilateral pneumonitis. In time the DLCO returned to normal in most patients.

4. Ventilation

The tidal volume decreased and the respiratory frequency increased in most subjects, giving a rise in minute volume ventilation per minute.

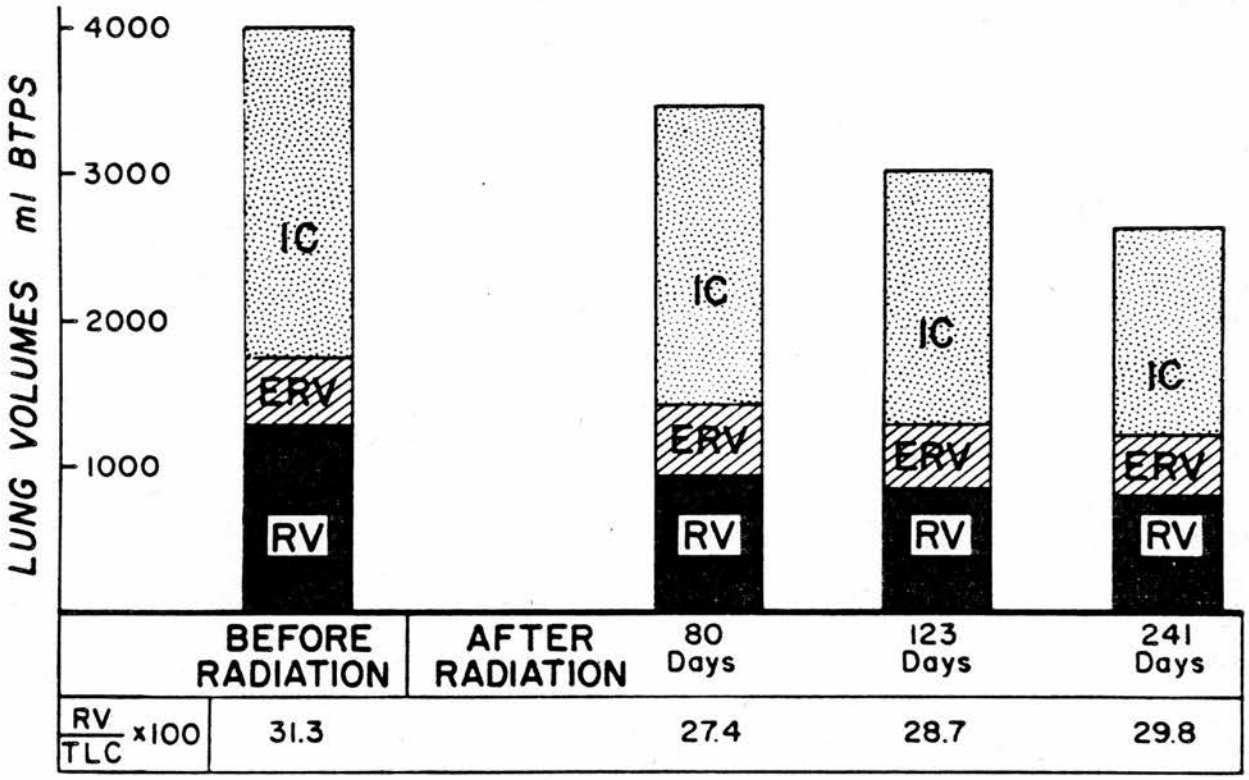


Figure 3

Lung volumes in ml BTPS before irradiation and at different intervals after irradiation in 4 subjects with unilateral radiation pneumonitis. (After Emirgil and Heinemann, 1961).

5. Mechanics of breathing

The maximal breathing capacity (MBC) was decreased in proportion to the degree of involvement. Pulmonary compliance was reported to be reduced progressively in some patients. The mean pulmonary resistance to air flow (flow-resistance) was slightly elevated in several subjects.

These authors indicated that irradiation of the chest, using a 2 MeV unit, with a tumour dose of 4400-5000 roentgen over 36-39 days, is complicated by a fall in lung volumes, an impairment of the diffusing capacity and an increase in the work of breathing at 80-200 days after irradiation. They also suggested that tests such as lung volumes and diffusion capacity are more sensitive than radiologic changes in anticipating clinical radiation pneumonitis. Thereafter several authors have studied the effects of radiation therapy on pulmonary function in carcinoma of the lung.

Voutilainen, Mahonen and Heinonen (1962) measured the vital capacity (VC), total lung capacity (TLC), residual volume (RV), function residual volume (FRV), maximum breathing capacity (MBC) and the diffusing capacity for carbon monoxide (DLCO) of 15 patients with bronchogenic carcinoma treated by radiotherapy. Their measurements were made before radiotherapy and were repeated immediately and at 3, 6 or 9 months after radiotherapy. They found that there was reduction in the functional residual volume (FRV) and DLCO in those cases who had abundant fibrotic changes due to irradiation, as shown on the chest x-ray. These results

were confirmed by Brady, Germon and Cander (1965) who found that reduction in the single breath diffusing capacity for carbon monoxide (DLCO) was the single and most significant change at 4 weeks after radiation therapy (median dose of 5200 rads over median elapsed time of 34 days) in 14 patients with carcinoma of the lung. In 1968, Germon and Brady studied the physiological changes before and after radiation treatment for carcinoma of the lung in 30 patients. Chest x-ray and pulmonary function measurements were made prior to therapy and at 1, 3, 6, 9 and 12 months after irradiation. They found that the vital capacity (VC) generally increased at one month interval and progressively decreased thereafter. The residual volume (RV) was found to decrease in the majority of their patients after radiotherapy. The diffusing capacity measurements were reduced in all except 5, at the one month study, but at 3, 6, 9 and 12 months further reduction of a lesser magnitude was noticed. On the other hand, the lung scan results [using I^{131} serum albumin aggregated (MAA I^{131} human)] before radiotherapy showed areas of abnormally reduced pulmonary capillary blood flow. These areas showed further reduction after radiotherapy. These authors suggested that the lung function changes were non-specific changes and that alterations in the capillary blood flow and the resultant tissue changes were initiated by the co-existing tumour and aggravated by the radiation therapy.

However, in 1969, Cudkowicz, Cunningham and Haldane, studied a group of 36 patients with breast cancer treated

either with simple or radical mastectomy followed by Cobalt-60 radiotherapy. Pulmonary function tests were performed after 9 treatments, at completion of irradiation and at 3, 6, 12 and 18 months after radiotherapy. They compared their results with a group of normal women of similar age. These authors reported progressive reduction in physiological dead space, reaching a maximum decline at 12 months following irradiation with a partial recovery thereafter, but the reduction in the diffusing capacity was rapid and recovery began at 18 months and improvement recorded later. Residual volume was found to be raised immediately at the end of radiotherapy, but rapidly returned to normal. These results showed the combined effect of mastectomy and radiotherapy, but without having control values for these measurements before therapy.

In 1970 Boushy, Helgason and North studied 42 patients with bronchogenic carcinoma treated with radiotherapy. All had pulmonary function studies and chest x-rays before radiotherapy and 33 had repeated studies after completion of therapy (i.e. at about 7 weeks). Their results showed that there was a significant reduction in the diffusing capacity for carbon monoxide (DLCO) after irradiation and a reduction in the pulmonary resistance at expiration; whereas a significant increase in the minute ventilatory ventilation was reported after radiotherapy in these patients. These results were thus confirmed by other reports.

Moreover, studies of lung function after upper mantle-field irradiation for Hodgkin's disease were reported in 1973 by Høst and Vale who studied 17 patients

before radiotherapy and at 2 and 15 months after radiotherapy. They found a reduction in vital capacity following radiotherapy which was confirmed by Evans, Sagerman, Ringrose, Howland, Auchincloss and Bowman (1974) who studied 11 patients with Hodgkin's disease treated in the same manner. A reduction of total lung capacity (TLC) and residual volume (RV) caused by radiotherapy was also found by Høst and Vale (1973), as shown in Figure 4.

Changes in pulmonary compliance caused by ionizing radiation have been studied in rats by Nairmark, Newman and Bowden (1970). They studied the deflation pressure volume curves in the irradiated lungs and compared them with those of the control lungs. They found that the compliance of the lungs was normal one month after radiation, but thereafter a progressive reduction in compliance was recorded, associated with the severity of the radiation reaction in the lung. This reduction in compliance of the irradiated rat lungs was confirmed by Shrivastava, Hans and Concannon (1976) at six weeks after irradiation, when the dose of irradiation delivered to the rat lung exceeded 1500 rads.

On the other hand, Teates in 1968 studied the pulmonary blood flow changes following a unilateral right thoracic irradiation of 3 dogs. A mid-lung dose of 3000 rads was directed to the entire right lung, but sparing the left lung in 3 doses over a 5 day period. A lung scan and thoracic x-ray were carried out prior to irradiation and at frequent intervals up to about 400 days after irradiation. Scans were obtained using I.V. injection of 100 microcuries of I^{131}

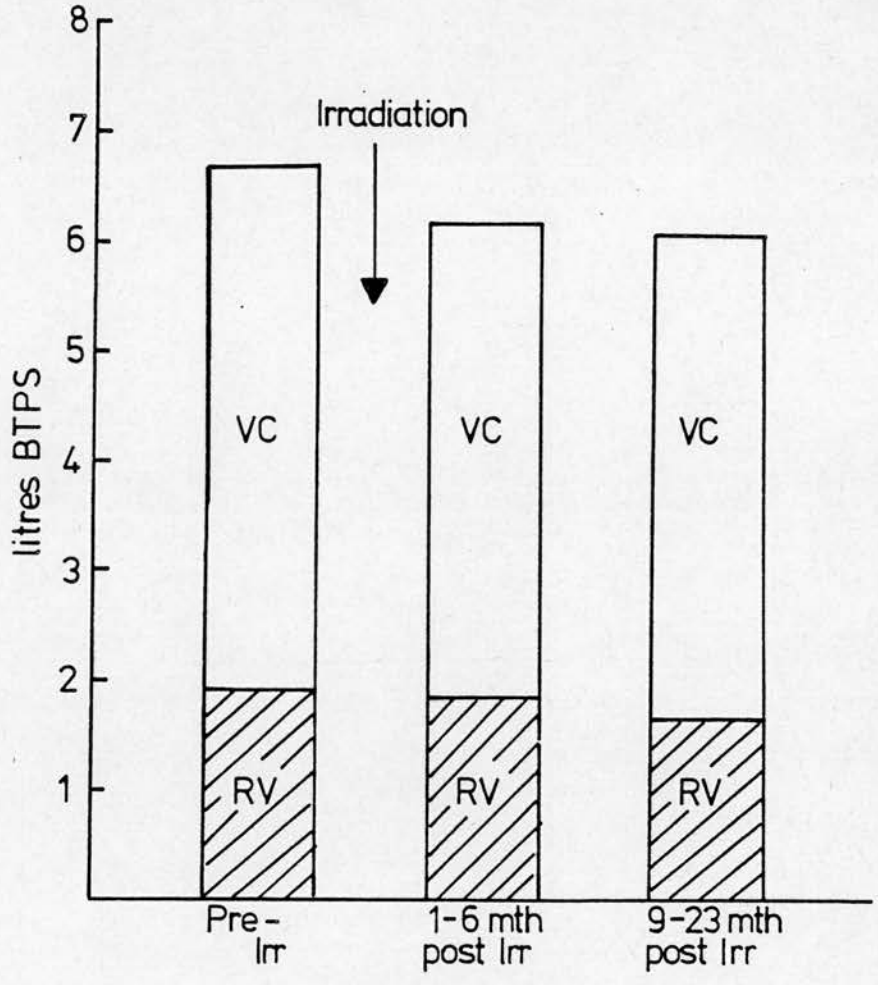


Figure 4

The lung volume changes [vital capacity (VC) and residual volume (RV)] before and after upper mantle-field irradiation for Hodgkin's disease in 17 patients. (After Høst and Vale, 1973).

macroaggregated human albumin. Pulmonary arteriograms were also performed at about 400 days after irradiation in each dog. The total scan density of the right lung was compared to the total scan density of both lungs and the values for estimated percentage artery perfusion of the right lung were calculated. The estimated blood flow to the right lung prior to irradiation averaged 49.5% of the total lung perfusion in the 3 animals, and by 52-109 days after irradiation the flow was markedly reduced, as shown in Figure 5. Loss of volume of irradiated lung was noticed on the arteriogram. The pathology of the irradiated lung and the chest roentgengrams confirmed the presence of radiation pneumonitis. The results showed no significant improvement in the blood flow as the pneumonitis cleared, leaving the late fibrotic stage. Johnson, Sagerman and Dombrowski (1970) also confirmed the reduction in pulmonary blood flow following irradiation of the entire right lung in Swiss mice, using an injection of a suspension of I^{131} labelled macroaggregated human serum albumin (radioactivity content was measured by a scintillation counter). The results were expressed as Pulmonary Perfusion Ratio (PPR) of the irradiated lung to the control lung. They concluded that the pulmonary ischaemia caused by radiation is an irreversible process and that the intensity of this ischaemia is affected by both the size of the radiation dose and also by the length of survival following treatment. Korsower, Skovron, Ghossein and Goldman (1971) studied pulmonary artery perfusion in 44 rabbits, following a single exposure of 3000 rads to either hemithorax, through an anterior field

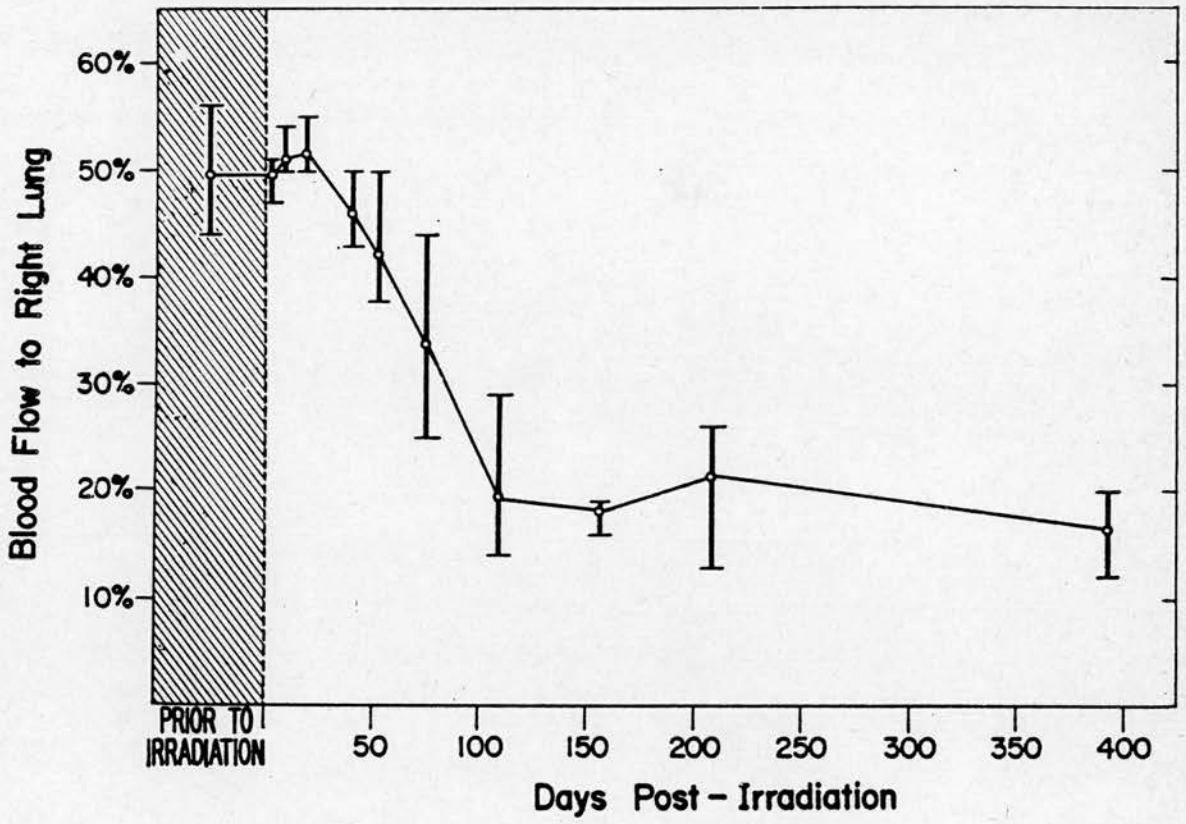


Figure 5

Estimated percentage of pulmonary blood flow to the irradiated right lung. The average values for the 3 animals and their ranges are indicated. (After Teates, 1968).

over a period of 15-18 minutes. Lung scans (using I.V. injection of I^{131} MAA) and chest x-rays were performed on each animal prior to irradiation and 2 hours, 24 hours and 48 hours after irradiation, some animals also being studied 3 weeks and 2 months following irradiation. They found the chest x-ray to be normal before therapy and at 2, 24 and 48 hours after irradiation; whereas the lung scan showed moderate to marked reduction in pulmonary arterial perfusion of the irradiated lung in 52% of the rabbits (as compared to the control lung and to the lung scans prior to irradiation) as soon as two hours after irradiation. Pulmonary angiograms performed (on 5 animals) at that time demonstrated delayed opacification in pulmonary artery and vein on the irradiated side, indicating reduced blood flow on that side. However, perfusion was reported to return to normal at 24 hours, 48 hours and 3 weeks, as assessed by lung scans. Yet, the 5 rabbits studied two months after irradiation showed marked reduction in pulmonary artery perfusion on the irradiated side. Later on, Freedman, Lofgren and Kligerman (1974) confirmed the reduction in perfusion 2-4 hours after a lethal dose of irradiation (4500-6000 rads), but also reported early hyperemia with increased perfusion during the first few days after a single dose of irradiation (1500 and 3500 rads) to the right lung of their experimental rabbits. These results were confirmed by Fernholz, Elfes, Frik and Breining (1977). A reduction in perfusion in the lung scans of these animals was reported at 3 weeks and onward, this reduction reaching a level of 50% of the base-line at about

the hundredth day after irradiation (Figure 6).

Fernholz et al (1977) found that perfusion returned to normal between the third and tenth day after a single dose of irradiation, but by the twenty-first day the perfusion was found to be diminished in the affected lung with a corresponding increase in perfusion in the non-affected lung. On the other hand, changes in pulmonary artery perfusion in humans following thoracic irradiation have also been reported (Johnson, Sagerman and Jacox, 1968; Goldman, Freeman and Ghossein, 1969; Bake, Bjure, Johansson, Rosengren and Stiksa, 1969; Shinohara and Arkiawa, 1972; Abe, 1974), seven out of the 16 patients (with intra-thoracic tumours treated by radiotherapy) studied before and after radiotherapy being found to have ischaemic changes or an increase in the pre-existing ischaemia as shown by the lung scan with I^{131} macroaggregated albumin, but the x-ray signs of radiation damage to the lung or pleura were less marked in these patients (Johnson et al, 1968). These results were confirmed by Goldman et al (1969) who studied 36 patients undergoing thoracic irradiation before treatment, at the completion of the treatment and at several intervals thereafter ($1\frac{1}{2}$, 3, 6 and 12 months after radiotherapy). One third of their cases had evidence of radiation pneumonitis and/or fibrosis with changes on either chest x-ray or in a perfusion scan with a defect suggesting radiation pneumonitis. These ischaemic changes shown in lung scans were greater than the fibrotic infiltrate seen on chest x-ray in four cases studied at 12 months after radiation.

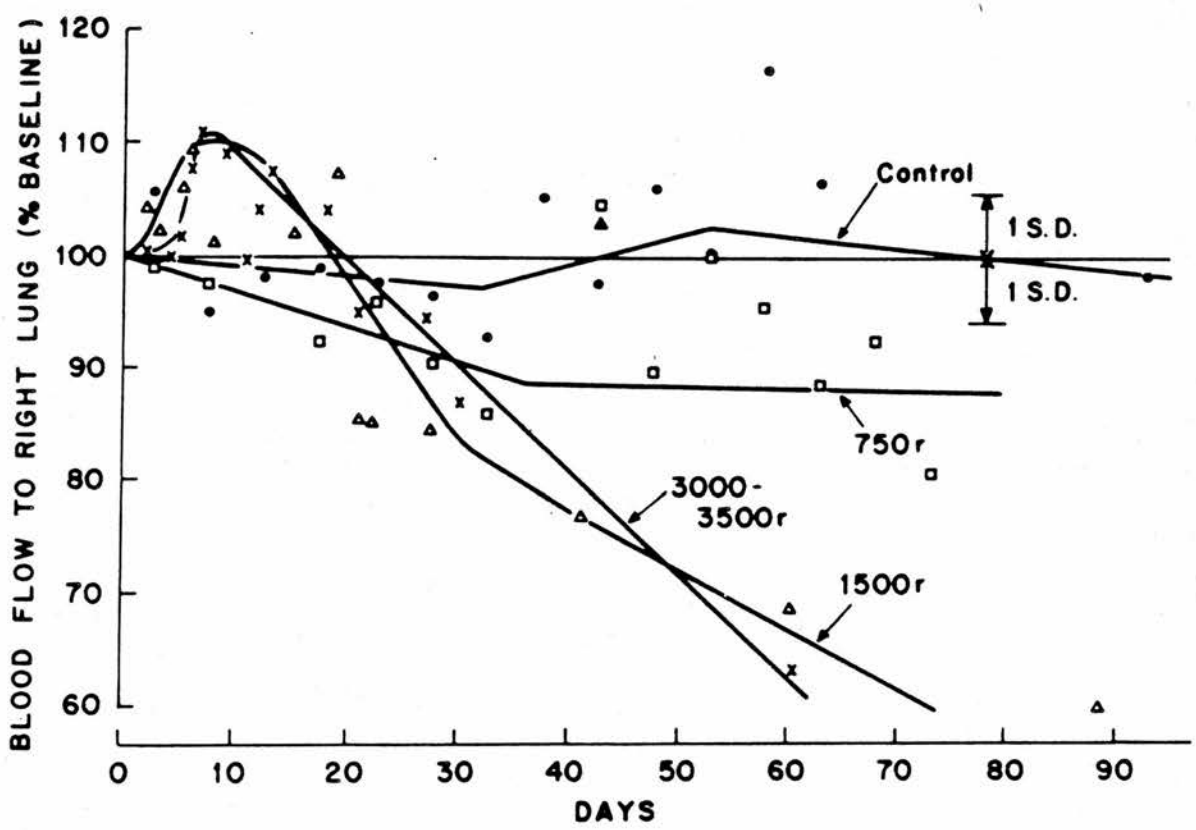


Figure 6

The reduction in the blood flow to the right irradiated lung as a percentage of the control lung in the rabbits following different doses of irradiation. Early hyperemia, with increased perfusion during the first few days, was reported. (After Freedman et al, 1974).

On the other hand, Bake et al (1969) studied the pulmonary perfusion as part of their regional lung function studies in patients with a local pulmonary radiation reaction. They studied nine patients with carcinoma of breast treated with mastectomy and conventional radiotherapy. The first study was carried out when the patients showed radiological changes (i.e. about 2-4 months after treatment); the second study was performed at 1-4 months later (i.e. when radiographic changes and clinical symptoms diminished). Their studies included quantitative evaluation of tissue density using gamma radiation from Cs^{137}, lung scan with I^{131} labelled MAA (200 mCi) and a $xenon^{133}$ scan (regional ventilation and perfusion scan). They found that there was a reduction in both perfusion (lung scan and $xenon^{133}$ scan) and ventilation in the irradiated region of the affected lung, as compared to the other lung in their patients showing x-ray changes after radiotherapy. However, in the second study (1-4 months later, when x-ray changes were resolving) there was no difference between the perfusion or ventilation of the affected lung, as compared to the other side, but the ventilated lung volume of the affected side was less than the unaffected. Thus, these authors concluded that the total ventilation and perfusion to the affected side was reduced. Moreover, Shinohara and Arikawa (1972) reported that the relative pulmonary arterial blood flow reduces in the irradiated side of the lung before the occurrence of radiation pneumonitis in patients receiving

incidental pulmonary irradiation for post-operative radiotherapy for breast cancer. They concluded that lung scanning using I^{131} labelled MAA could be used for earlier detection of radiation pneumonitis. These findings were confirmed by Abe (1974) who carried out quantitative radioisotope scanning (using I.V. I^{131} MAA) before and after radiation therapy in 25 patients receiving post-operative irradiation for breast cancer. He reported that the pulmonary blood flow reduced after irradiation and that the degree of reduction was proportional to the post-irradiation changes in the chest x-rays. He found also that the reduction of the blood flow occurred before the alteration of the chest x-rays.

In addition, recently Prato, Kurdyak and Saibil (1977) studied 18 patients who had received post-operative Co^{60} radiotherapy for their breast cancer. They studied each patient once from 3 months to 6.7 years after the start of their radiation therapy. These patients were chosen to be free of pulmonary or metastatic disease and had simple or modified radical mastectomy followed by 5 field radiation treatment (anterior and posterior supraclavicular and axilla, two parallel opposed tangential fields to the chest wall and an anterior field to the internal mammary glands) using Cobalt 60. Another group of 20 patients who had the same operation about one month previously, but who had not started their radiation therapy, were also clinically free from pulmonary or metastatic disease, and were used as a control group.

These authors measured both static and dynamic lung volumes (TLC, FRC, VC, ERV, FEV_1, FVC), maximum breathing capacity (MBC), maximum end-expiratory flow from 75% to 25% of vital capacity (MMEF) and blood gases and pH using arteriolized capillary blood. Clinical examination and chest x-ray were also carried out at this time. Regional lung function measurements were also made, using radioactive Xe^{133} in the supine position, measuring ventilation/unit lung volume ($[\dot{V}]r$), blood flow/unit ventilated lung volume ($[\dot{Q}]r$), regional total lung capacity $(TLC)r$, blood flow to the ventilated alveoli ($\dot{Q}r$) and the ratio of residual volume to total lung capacity (RV_r/TLC_r). These authors found that values for FEV_1, FVC and ERV to be significantly reduced in the irradiated group as compared to their control group, but that the arterialized capillary blood gas tensions were within the normal range. They calculated their indices of regional lung function as a ratio of that variable in the irradiated apex to an equivalent area of the opposite (untreated) lung apex and compared these ratios (i.e. irradiated/non-irradiated) with those of the control group. They found that the ratio of ($[\dot{Q}]r$), ($[\dot{V}]r$), $(\dot{Q})r$ and $(TLC)r$ was significantly lower in the irradiated group as compared to those of the control group; whereas the RV_r/TLC_r ratio was significantly higher. They also found that their radiographs under-estimated functional radiation damage and that in each patient blood flow changes were either more severe or equally severe as the changes in TLC_r. On the other hand, some of

their cases had better function in the irradiated apex, thus suggesting that these variations could be due to pre-existing physiological differences and/or the response to radiation treatment. They therefore suggested that it is necessary to study patients before and at various times after treatment.

In a further study, the same authors (Prato, Kurdyak, Saibil, Rider and Aspin, 1977) studied 25 patients irradiated for breast cancer (using the same technique as in their previous work). They repeated the same total measurements and regional measurements of pulmonary blood flow and ventilation before and at various times (from 16-407 days) after radiotherapy and also estimated the dose in the irradiated apex from the 5 radiation fields and found that it varied from between 846 to 1536 rets (rad equivalent therapy). Thus, they suggested that since the pulmonary tolerance was thought to be between 800-1000 ret (Wara, Phillips and Mangolis, 1973), then most of their patients received more than this dose. They found that only FVC and ERV were significantly reduced on the average values measured 100 or more days after the start of treatment, by comparison to their pre-treatment values. The pre-treatment regional lung function was compared to the average of the values measured 60 days or more after radiotherapy. They found that radiation caused marked reduction in the regional blood flow to the ventilated alveoli ($\dot{Q}r$) at all times after treatment and a similar reduction was also found in TLC_r. Furthermore, the

reduction in ventilation ($[\dot{V}]r$) and perfusion ($[\dot{Q}]r$) was not very marked and shortly after irradiation the reduction in ($[\dot{Q}]r$) was smaller than ($[\dot{V}]r$) with a subsequent recovery, and beyond 300 days the average values of ($[\dot{Q}]r$) and ($[\dot{V}]r$) were virtually the same. However, values at 232 days showed a picture of under-perfusion rather than under-ventilation. The results of their regional studies are shown in Figure 7.

The authors also estimated the perfusion by two techniques; by Xe^{133} injection and from the injection of Tc^{99m} macroaggregated albumin in 5 patients at 42 days or more after radiotherapy. They found that these two techniques gave very similar estimates of the amount of blood flow damage. Moreover, these authors suggested that changes in blood flow ($[\dot{Q}]r$) preceed and are more severe than changes in the volume of ventilated tissue (TLC_r) and that the alveolar damage results from the direct effect of irradiation.

On the other hand, these authors reported no relationship between clinical symptoms and either radiological changes or lung function measurements. They suggested also that prediction of those individuals who are going to develop severe pulmonary complications could be made by measuring the regional lung function at the end of 3 weeks or more following radiotherapy.

In general therefore, pulmonary function changes following irradiation of the lungs (animals or humans) could be summarised (Gross, 1977):

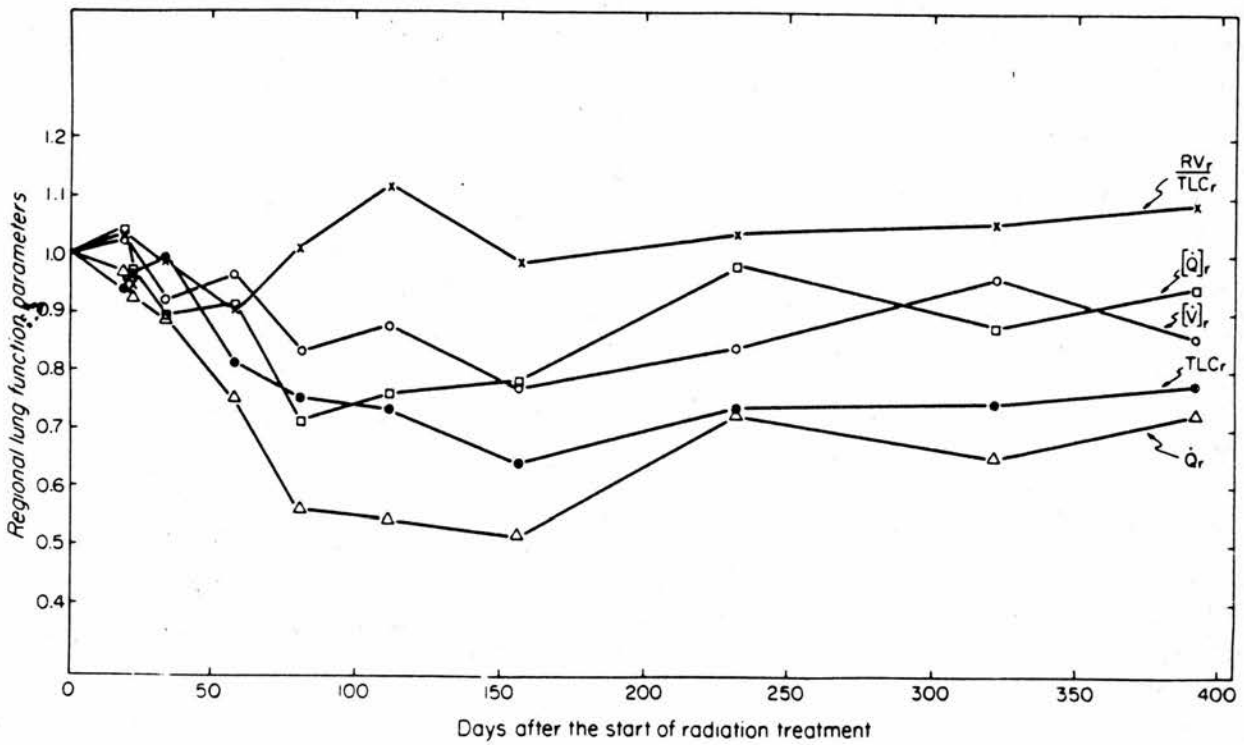


Figure 7

The regional lung function ($\frac{RVr}{TLCr}$, $[\dot{Q}]r$, $[\dot{V}]r$, TLCr and $\dot{Q}r$) in 25 patients after post-operative Co^{60} radiotherapy for breast cancer. Each point represents the average value of that parameter for a group of 6 patients, plotted at the mean time after the start of radiotherapy. All measurements are normalized to pre-irradiation values. (After Prato et al, 1977).

I Lung volumes: a symmetrical reduction in all compartments (TLC, VC, RV, FVC) observed at 11 weeks after radiation and which, in some cases, may develop earlier and may persist for 5 years or for as long as 14 years.

II Transfer factor for carbon monoxide (TCO): probably indicating impaired gas exchange reduced at 4-11 weeks after radiotherapy and may remain reduced for 6-18 months, then may gradually return to normal. These changes have been associated with mild arterial hypoxia and an increased alveolar to arterial oxygen gradient.

III Lung mechanics: a reduction in compliance related to both dose and time has been seen in both animal and human studies, coinciding with radiological pneumonitis and progressing to fibrosis. Maximum breathing capacity (MBC) has been reported previously to be reduced, but Prato et al (1977) reported a non-significant increase in MBC. Airway resistance has been reported to be either normal or slightly increased. The elastic work of breathing is increased as a result of the reduced compliance.

IV Reduction in pulmonary perfusion: has been shown on both clinical and experimental studies to occur in the irradiated lung. Moreover, hypoperfusion was found to be confined to the irradiated lung by both lung scans, and by regional pulmonary perfusion studies with Xe^{133}, with reduction in perfusion involving the irradiated region. These perfusion changes were reported to appear one to two months after irradiation and presumed to result from

the structural effects of radiation on the pulmonary capillary bed.

Breast cancer is a common malignant disease and, as mentioned above, since radiation pneumonitis occurs mainly following radiotherapy for breast carcinoma, it therefore follows that the effect of radiation on lung function (regional and total), in otherwise normal lung, can be studied in these patients; whereas such a study in women involving radiation for experimental purposes only would clearly be unethical.

vi) Carcinoma of the breast

Carcinoma of the breast principally affects women aged between 40-50 years. The tumours characteristically spread:

a) locally to the neighbouring tissues such as pleural involvement through the chest wall

b) lymphatic, either by emboli or by permeation to involve the axillary, supra-clavicular, internal mammary lymph nodes and also the opposite breast and the mediastinal lymph nodes

c) haematogenous with skeletal, liver and brain metastases

Histopathological varieties of breast carcinomas include (Bruce and Hayward, 1975): scirrhous carcinoma (63%), anaplastic carcinoma (17%), intraduct carcinoma (8%), atrophic scirrhous carcinoma (5%) and others.

In the present studies the carcinoma was staged clinically at the time when the patient was first seen.

The Manchester staging system was in use until 1958, this then being replaced by the International TNM (Tumours, Nodes, Metastases) system until 1973, when the Union International Contra Cancer and the American Joint Committee on Cancer Staging (UICC/AJC) issued an agreed system of staging (TNM, 1973). The International Staging is summarised as follows (Langlands, 1976):

Stage I	A tumour of 5 cm or less ± partial fixation to overlying skin
Stage II	As in Stage I, but associated with palpable mobile homolateral axillary lymph nodes
Stage III	The remainder
Stage IV	Associated with blood borne metastases

vii) Treatment of breast cancer

The methods of treatment depend on the stage of the disease. Stage I and stage II are generally treated by simple or radical mastectomy and/or radical radiotherapy. However, it was found that when radical post-operative radiotherapy is used in the treatment of stage II carcinoma of the breast, a modified simple mastectomy was preferable to a radical mastectomy (Brinkley and Haybittle, 1971). On the other hand, the more advanced stages may be treated by simple mastectomy, radiotherapy or endocrine therapy in those tumours which are hormone dependent (Bruce and Hayward, 1975) or chemotherapy (Fisher, Carbone, Economou, Frelich, Glass, Lerner, Redmond, Zelen, Band, Katryck, Wolmark and Fisher, 1975).

The curability of treated breast cancer by simple and/or radical mastectomy and radiotherapy was studied in 704 women in the Cambridge area from 1947 - 1950 (Brinkley and Haybittle, 1975). It was found that after 21 years the survival curve of breast cancer patients runs parallel to the expected survival curve of a similar normal population, as shown in Figure 8. However, in the South-East region of Scotland, in which some 500 cases of breast cancer are seen each year, from a population at risk (both sexes) of 1.25 million, the survival rate is shown to vary according to the size of the tumour (Langlands, 1976) (Figure 9). This region includes cases from Edinburgh, parts of Fife and parts of the Borders. Figure 10 shows the number of cases referred from 1973 - 1976 (Annual Report, Department of Radiotherapy - Edinburgh). The mortality rate of breast cancer in Edinburgh, Fife and the Borders, over the years 1972 - 1976, is shown in Figure 11 (Annual Report of Registrar General, Scotland).

The routine method of treatment of breast cancer is by simple mastectomy followed by radiotherapy (which is carried out whenever it is technically possible to do so). Simple mastectomy is performed in nearly all operable cases and also in many patients with locally advanced lesion, aiming for the removal of the involved tissue. Thereafter radiotherapy is given (at about two weeks after simple mastectomy) as the sole method of treatment of the regional lymph nodes. Thus, to treat the axillary node in continuity with the supra-clavicular nodes, two opposed fields are used. Moreover,

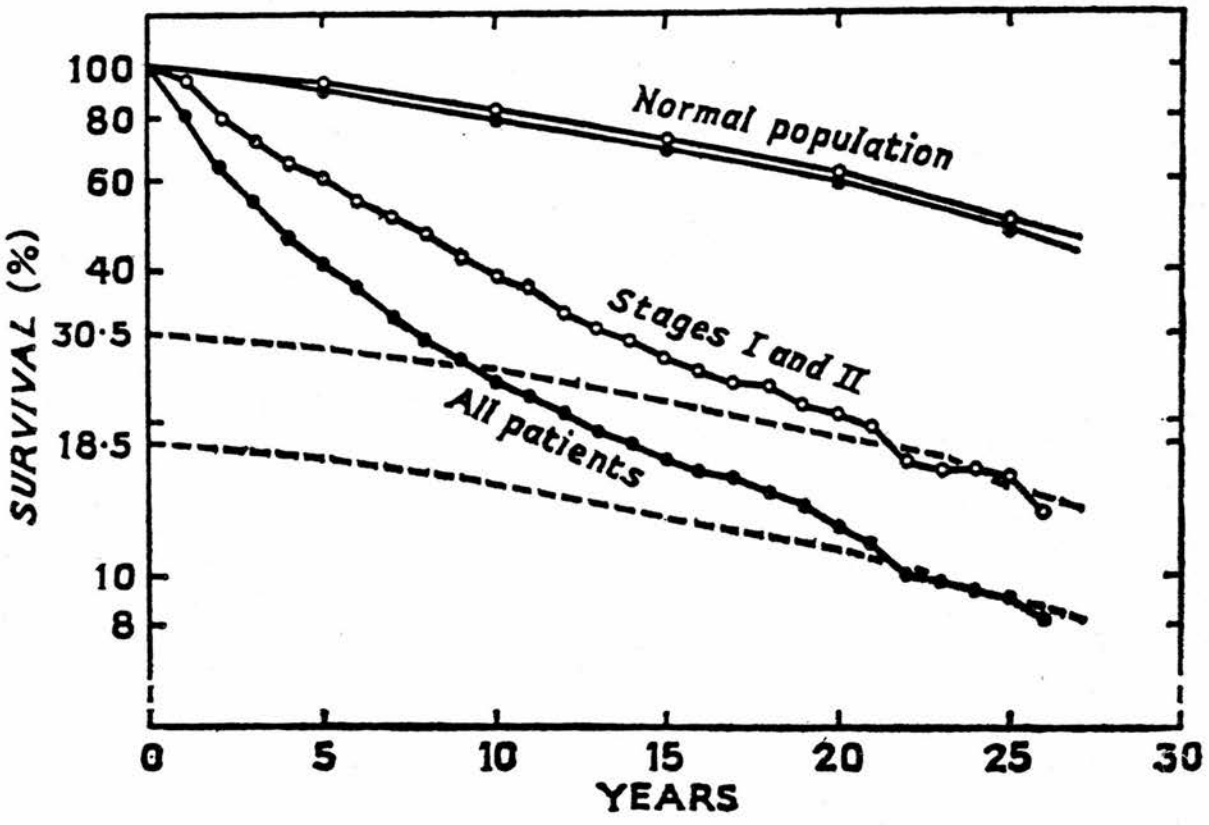


Figure 8

Survival rates after treatment of 704 women with breast cancer, compared with expected survival of normal populations of the same age distribution. (After Brinkley and Haybittle, 1975).

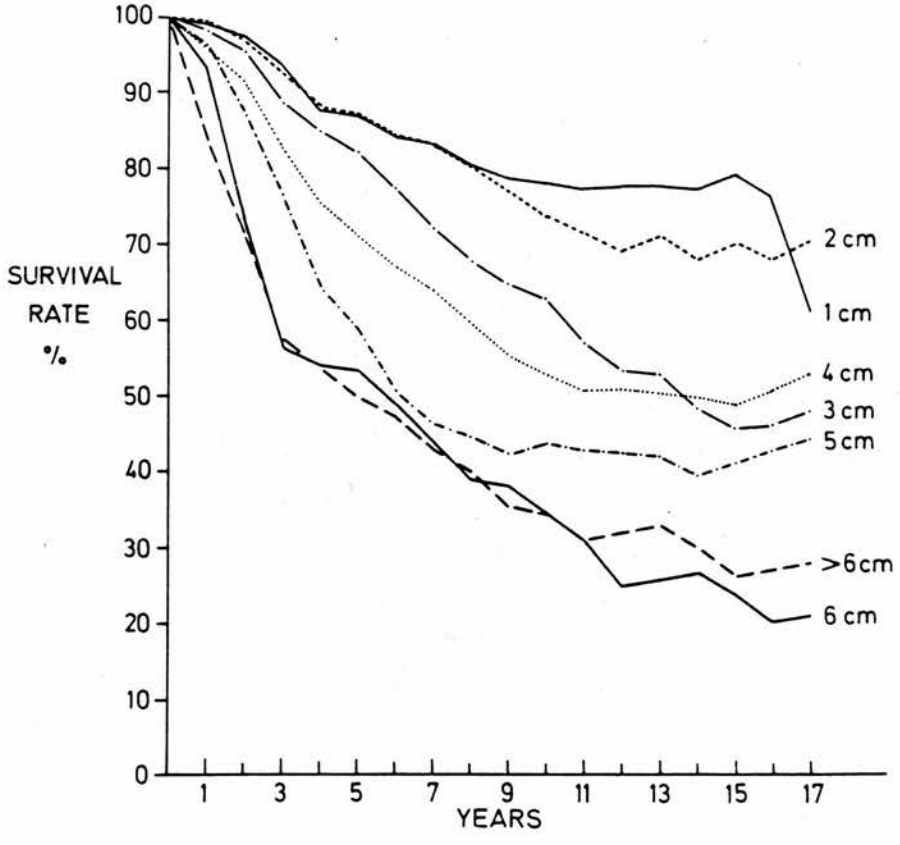


Figure 9

Age-corrected survival rates according to the size of the primary tumour on clinical examination. All cases treated by simple mastectomy and x-ray therapy. (After Langlands, 1977).

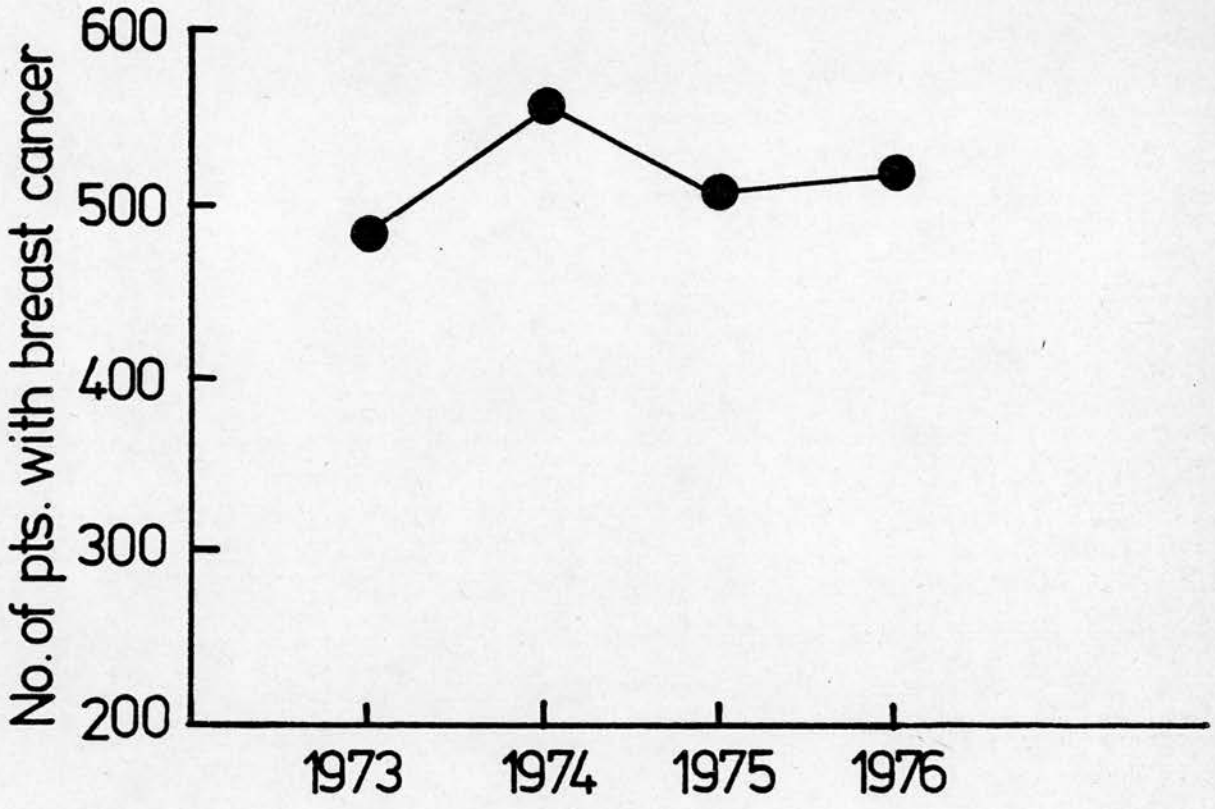


Figure 10

Number of patients with breast cancer referred to the radiotherapy department in Edinburgh from the South-East region of Scotland (Edinburgh, parts of Fife and the Borders), from a population at risk of 1.25 million.

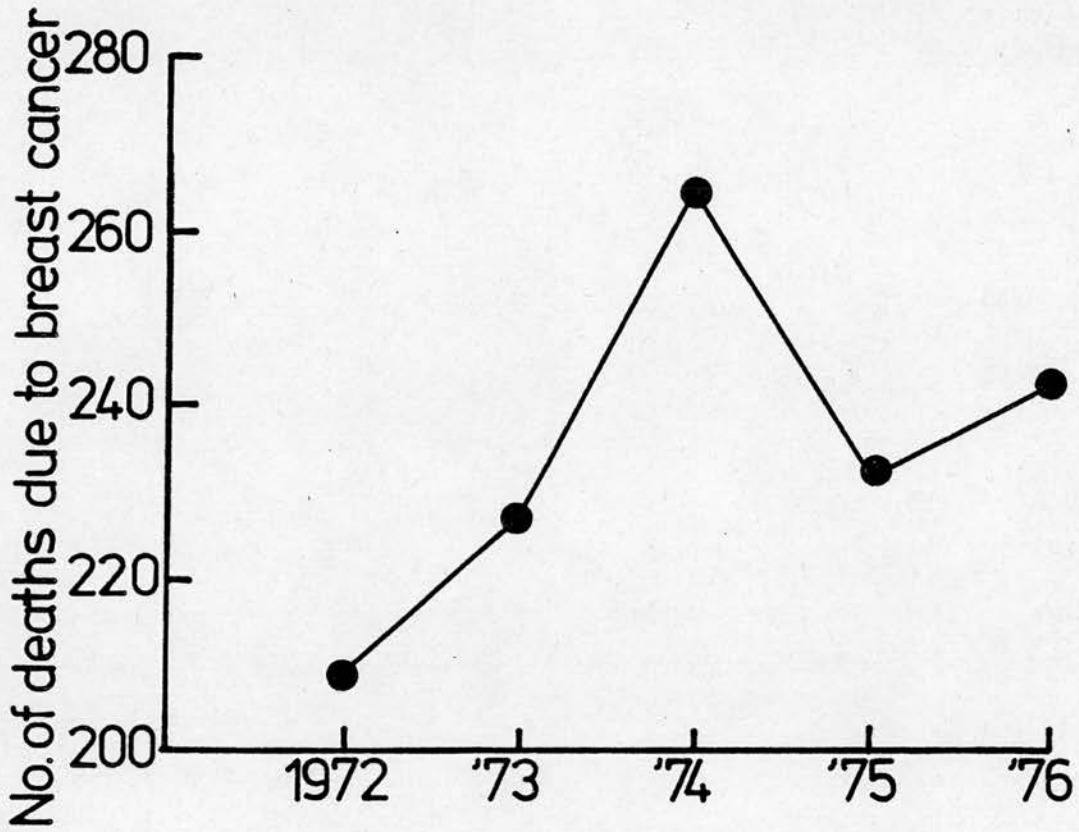


Figure 11

Number of deaths due to breast cancer from 1972 - 1976 in Edinburgh, Fife and the Borders region.

tangential fields are used to irradiate the whole thickness of the chest wall, including the pleura and the internal mammary nodes (McWhirter, 1955). The fields of radiotherapy are shown in Figure 12.

Field I is an anterior supra-clavicular one which extends downwards from the supra-sternal notch to the second costal cartilage (about 10 cm) and laterally to include the axilla (about 20-22 cm, as measured in each individual case).

Field II is a posterior supra-clavicular one which is about the same size as field I, but is angled to include the axillary nodes as well as the posterior clavicular nodes and is also positioned about 1 cm laterally away from the spinal cord. The dose given in these fields (I and II) is 4250 rads "to max".

Therefore fields I and II, which are parallel, semi-opposed fields, will include the apex of the lung. Thus, that volume of lung irradiated (which varies as the fields extend to about 4-6 cm from the apex of the lung) will receive a dose of 4250 rads "to max".

Fields III and IV are tangential parallel opposed fields (wedge corrected to allow for the shape of the chest wall). The size of each field is 10 x 15 cm. Furthermore, field III, given at 1 cm away from the midline, (i.e. into the opposite side) is angled at 60° from the vertical plane towards the body to include the internal mammary nodes as well as the chest wall thickness, pleura

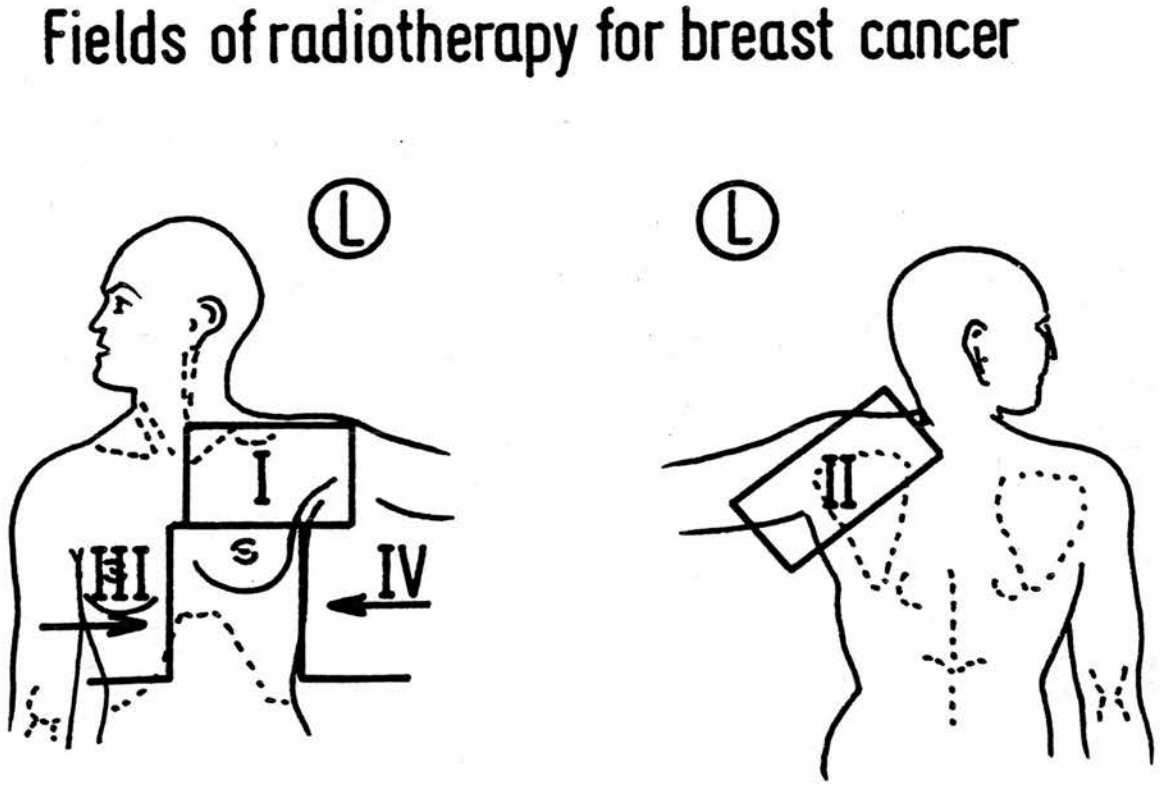


Figure 12

The four fields of radiotherapy:

I & II Anterior and posterior supra-clavicular

III & IV Tangential fields to the chest wall

and a thin layer of the anterior slice of the lung on the treated side (Figure 13). The dose given in this pair of fields is 4500 rads "to max".

Each pair of fields (I and II, III and IV) is treated on alternate days, thus 10 treatment fractions are given over a 4 week period.

Routinely, each patient is examined clinically before the start of radiotherapy and marking the area to be treated is usually made then. Furthermore, the marks are checked with an adjustable light beam which coincides with the x-ray beam on the linear accelerator (6 MeV) (Figure 14). The x-ray beam is given at a focus skin distance (FSD) of 100 cm.

A bolus (tissue equivalent material) is used with fields I and II and a bolus and wedge are used with fields III and IV in order to correct for the irregularities and any gap in the treated areas (Langlands, 1977).

As mentioned above, the upper part of the lung receives 4250 rads "to max" from fields I and II. Thus to calculate the exact dose of radiation given in these two fields, phantom experiments were made. From these experiments the percentage of dose of each field was calculated at different distances from the skin surface and with different field sizes. For examples, for field size 20 x 10 cm, using the 6 MeV linear accelerator, 100% of dose of one field is situated at 1.5 cm depth below the skin facing that field and the percentage of dose at different depths from the skin surface is shown in Figure 15. Furthermore, each point receives, in addition,

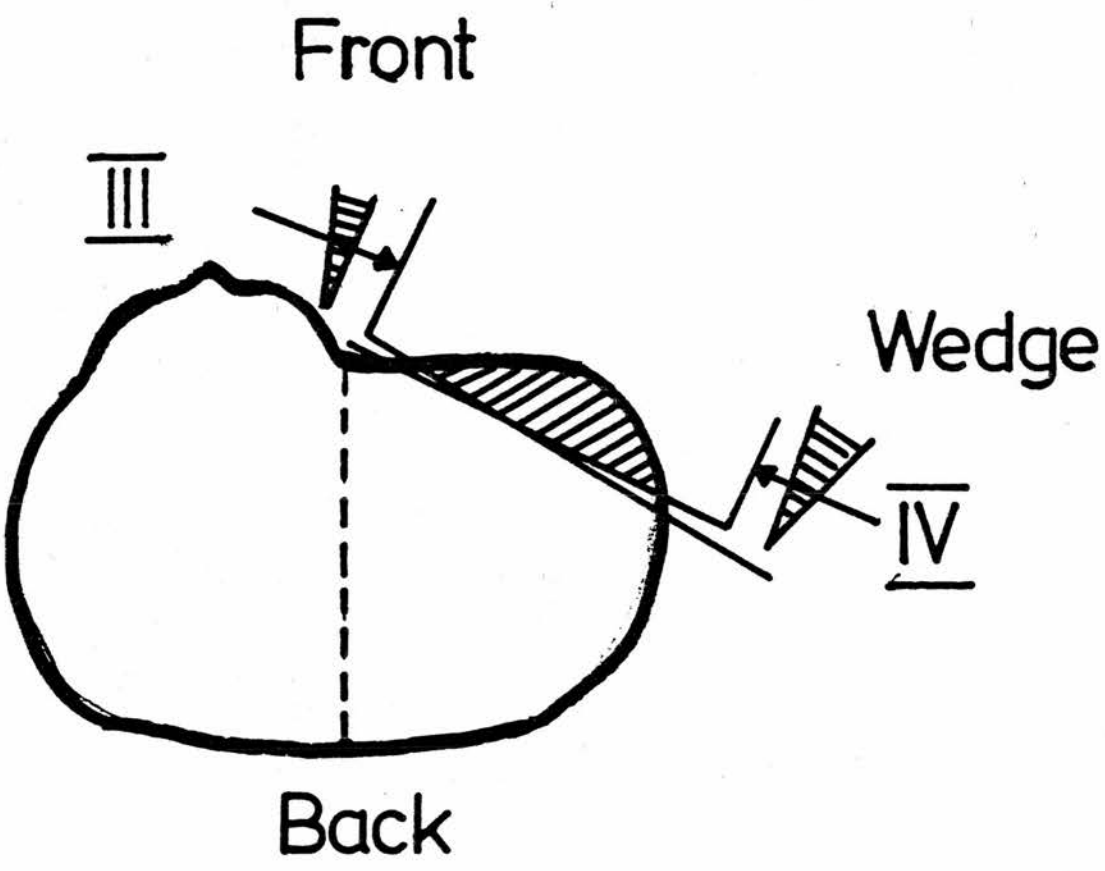


Figure 13

Showing the irradiated area by tangential fields III and IV in a cross-sectional diagram of a patient after mastectomy of the right breast.

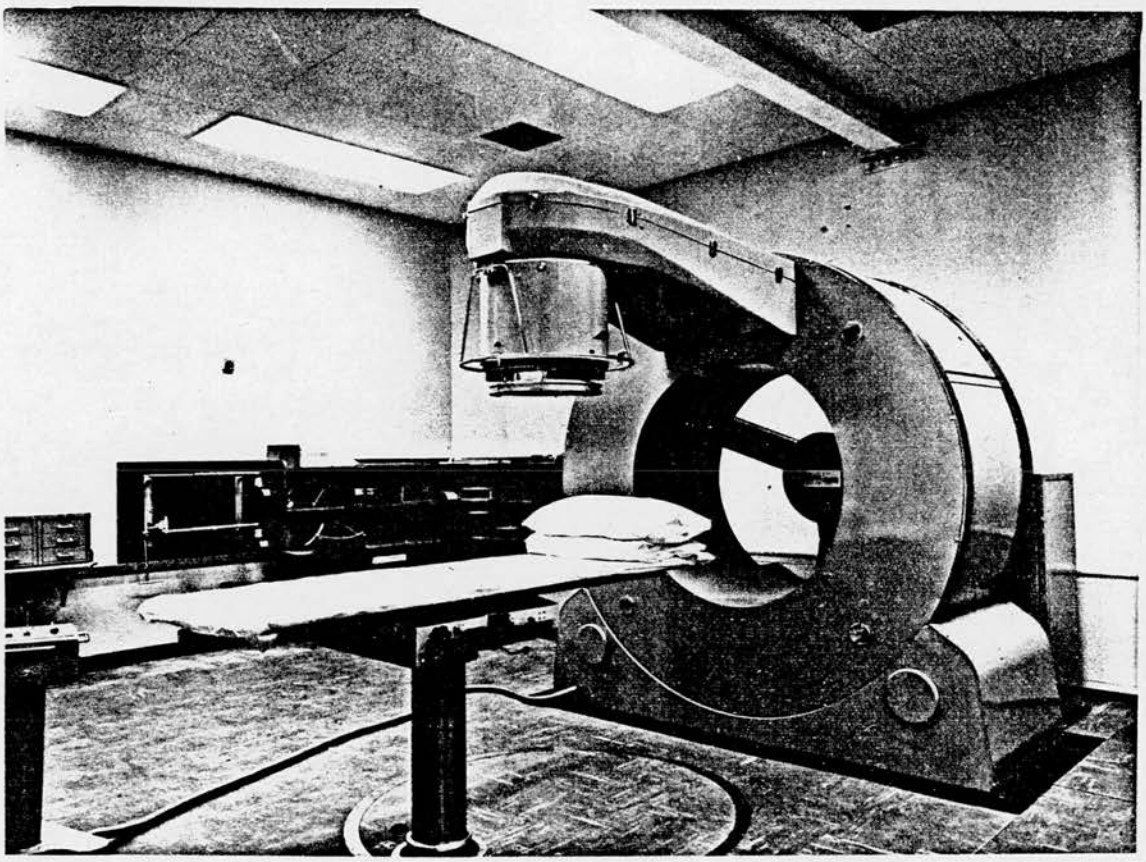


Figure 14

The (6 MeV) linear accelerator routinely used for the radiotherapeutic treatment of breast cancer patients in the South-East region of Scotland.

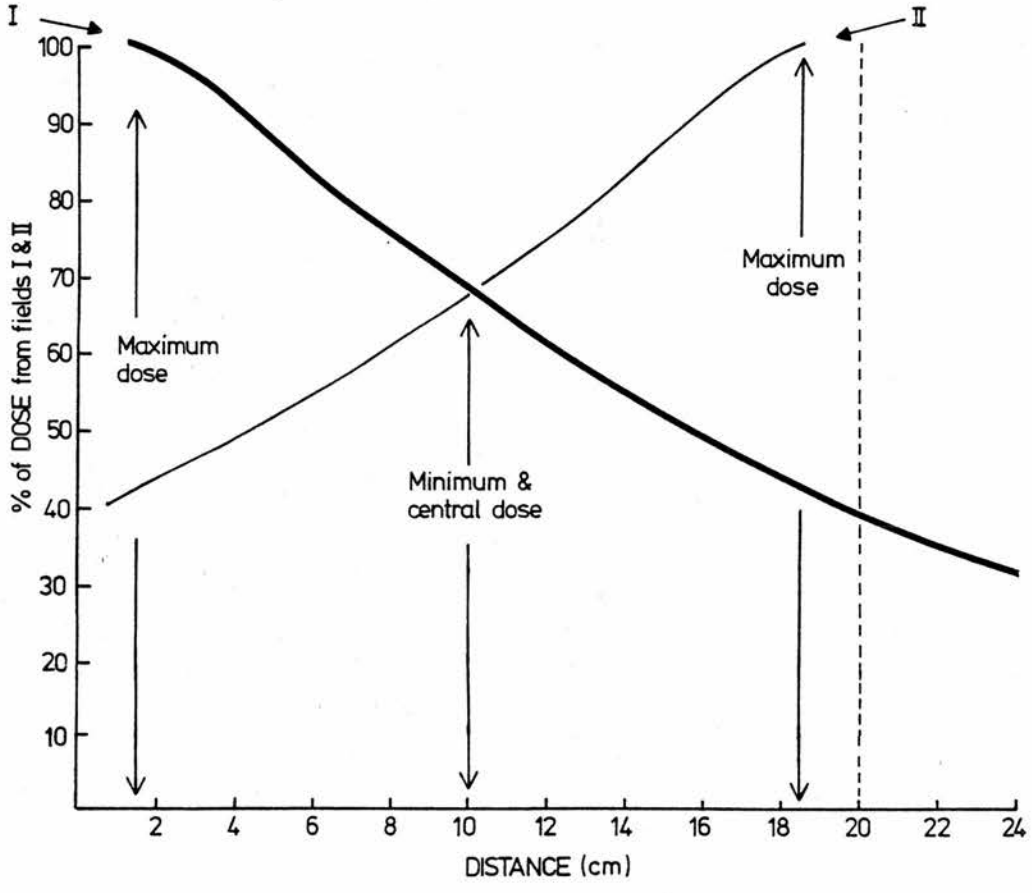


Figure 15

The thick line in this figure shows the percentage of the dose of field I as calculated at different distances from the skin surface for a field size of 20 x 10 cm. If the separation distance between the anterior and posterior borders of skin in a patient is 20 cm for example, as shown in the dotted line, the thin dark line then shows the percentage of dose of field II.

a certain percentage of the dose applied via the opposed field, depending on the separation distance between the anterior and posterior borders of the skin (which differ in each individual case). Thus, knowing that the maximal dose required at 1.5 cm below the skin surface is 4250 rads, this is made up of 100% dose from the first field + x% dose from the opposed field (where x% depends on the separation distance). The 100% dose in rads can then be calculated for each case, this being the actual treatment dose for each field. For example:

> If the anterio-posterior separation distance in a patient is 20 cm, then, as shown in Figure 15, the % dose at 1.5 cm depth = 100% + 42.5% = 142.5%; this is = to 4250 rads. Hence = 100% = 2982.5 rads, which is the dose used in each field

These measurements are always done before starting the treatment. Using the same idea, the minimal and central dose could be calculated, which is equal in this example to 68% + 68% = 136%, which is = to 4056.2 rads. Therefore in this case the lung apex receives a minimal radiation dose of 4056.2 rads as the lung is situated in almost the central part of fields I and II.

viii) <u>The Aim of this study</u>

As discussed above, this dose of radiation is more than the tolerance of the lung tissue to radiation, thus there is inevitably a radiation reaction in the lung. For example, for the last two years the Department of Medicine in the Royal Infirmary, Edinburgh has had

6 patients referred with symptomatic radiation pneumonitis following radiotherapy of their breast cancer. Figure 16 shows an x-ray of one of these patients. With such problems in mind, this study was carried out in order to answer the following questions:

I What are the effects of routine radiotherapy, given for breast cancer, on total and regional lung function in women with normal lungs?

II Does this routine radiotherapy have more effect on lung function in some of these women than in others?

In addition, the techniques evolved for this study, and the results obtained, would then allow the planning of a later study on the consequences of therapeutic irradiation of lung tissue as involved in the treatment of oat cell carcinoma of the lung and also provide guidance on the methods to be used in this later study to ascertain the role of previous disorders of lung function in determining the response of the lungs to radiotherapy.

Figure 16

An x-ray of a referred patient with symptomatic radiation pneumonitis at 6 months after radiotherapy of her breast cancer.

II METHODS

i) Patients and Protocol

The aim of this study, as discussed in the previous chapter, required that both total and regional lung function should be measured. Two groups of patients were studied. The first study involved a longitudinal sequential measurement in the same group of patients prior to radiotherapy, but after simple mastectomy and then subsequently at 1, 3, 6, 9 and 12 months after radiotherapy.

The second study was a cross sectional study in a group of patients at intervals from 1 - 14 years after radiotherapy as the technique and dose of mega-voltage radiotherapy for breast cancer in Edinburgh had not changed since 1963.

Ethical permission was given by three committees; the Surgical, the Radiotherapy and the Physicians Ethical Advisory Committees of the Royal Infirmary, Edinburgh.

In the first group the measurements were made before radiotherapy, but after recovery from simple mastectomy, when the tumour had been staged and the therapeutic decision taken by the surgeon and radiotherapist. These measurements were done to determine the pre-radiotherapy control values and to exclude any possible effect of the operation (i.e. the simple mastectomy) on lung function in this group. All the measurements were repeated at 1, 3, 6, 9 and 12 months following radiotherapy. Only 10 patients were included in this group as patients dealt with were treated by surgeons

and radiotherapists. Thus, first, permission of both had to be obtained for the submission of their patients to our study. Second, informed consent had to be obtained from these patients for this study, after full explanation of the purpose, the non-invasive nature of these studies and that these measurements were not related to their treatment, but were primarily for research purposes. These patients had only very recently been told that they had cancer of the breast, that they would have their breast removed and that they would have a course of radiotherapy to treat any possible cancerous tissue left after surgery. In these circumstances it might not have been surprising if they had refused to take part in the study as a 'guinea-pig'. Many of these patients thought that participation in the study was another problem they had to consider at this time of great stress and so rejected it. Third, some of the patients who gave their initial consent to participate in the study appeared to have a benign lesion at surgery and thus radiotherapy was not indicated. Another group comprised of patients who withdrew during the course of the study. One of the ten patients withdrew because the study was interfering with her working hours.

The age range of this group was 35-61 years, two being smokers and the rest non-smokers. The side of the cancer, and thus the simple mastectomy and radiotherapy, was on the right in three of these ten patients.

In the second study, a group of 48 patients who had previously had simple mastectomy and radiotherapy for their breast cancer between 1 and 14 years, were studied on one

occasion only. The age range of these patients was 36-73 years, 20 patients were non-smokers, 5 were ex-smokers and 23 were smokers. The side of cancer and thus the simple mastectomy and radiotherapy, was on the right in 29 of the 48 patients.

No difficulty was found in obtaining the patient's informed consent for this second study, perhaps because these patients had already had successful treatment.

In each study the MRC questionnaire (Medical Research Council Report, 1960) of respiratory symptoms was recorded for each patient, with their height and weight. Haemoglobin and white cell count were measured in venous blood. Overall and regional lung function were measured, as described later. In addition to these measurements, routine 6ft chest x-rays, postero-anterior (PA) and lateral (according to the side of radiotherapy) were taken and a standard 12 lead electrocardiograph (ECG) was carried out. The overall lung function included measurements of forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), measurements of lung volume, flow volume curves, measurement of airway resistance and specific airway conductance (sGaw) and measurements of transfer factor for carbon monoxide (T_{CO}).

ii) Overall lung function measurements

1. Forced expiratory volume at one second (FEV_1) and forced vital capacity (FVC) measurements

A "vitalograph" dry spirometer was used to measure FEV_1 and FVC. The characteristics of performance of the vitalograph have been reported by Drew and Hughes (1969).

The patients were seated and instructed to take a full inspiration, then close their lips around the mouthpiece and blow out as hard and as fast as possible and to continue blowing until no more gas could be squeezed from their chest. The volume at one second was recorded (FEV_1) and the total volume at the end of expiration was recorded also (FVC). Three measurements were made of the FEV_1 and FVC, the highest being taken. The results were reported as litres at ATPS and also expressed as percentage of FVC. The predicted values for our studies were calculated using the following formulae for females:

$$FEV_1 \text{ (litres ATPS)} = [(\text{height} \times 2.27) - (0.02 \times \text{age}) - 0.56] \pm 0.36 \text{ (S.D.)}$$

$$FVC \text{ (litres ATPS)} = [(\text{height} \times 3.78) - (0.019 \times \text{age}) - 2.60] \pm 0.34 \text{ (S.D.)}$$

$$FEV_1/FVC \text{ (\%)} = [(-0.261 \times \text{age}) + 92.1] \pm 5.4 \text{ (S.D.)}$$

(Cotes, 1968)

2. Lung volume measurements

Lung volume measurements were made with a "Fenyves and Gut" body plethysmograph, which is a pressure compensated flow plethysmograph (Figure 17). Pneumotachograph signals were integrated electronically, the resulting volume signals being recorded on an X-Y recorder. The pressure compensation in this body plethysmograph was made by adding an electrical signal (proportional to the pressure developed inside the plethysmograph) to the integrated flow signals to improve its

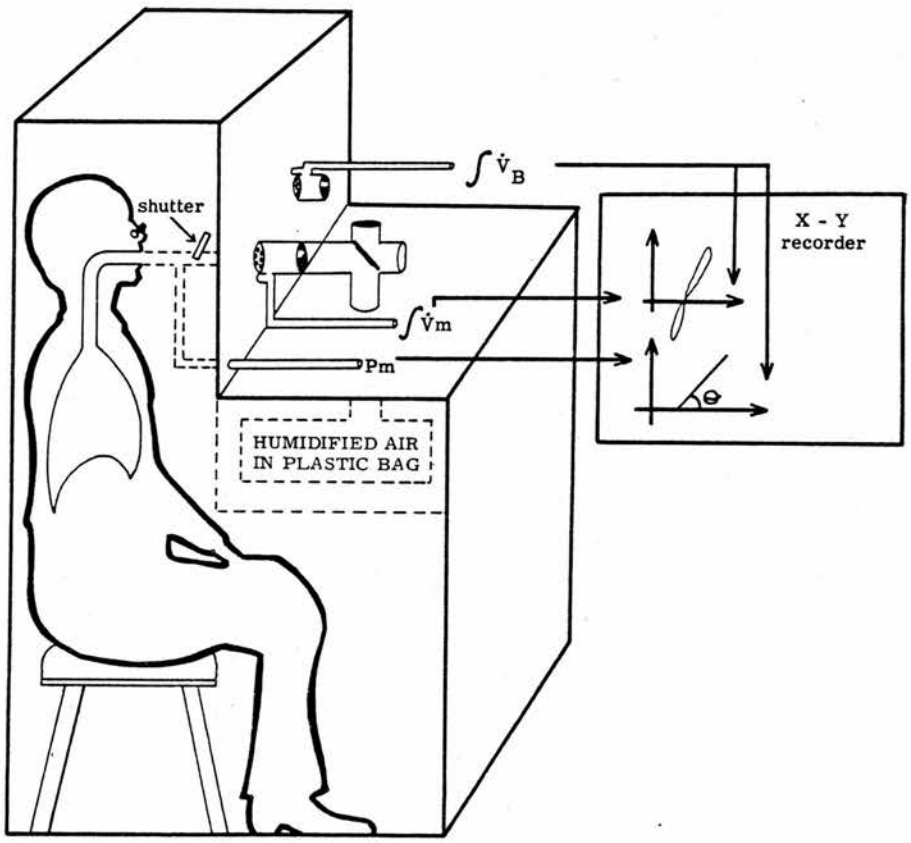


Figure 17

A schematic diagram of the patient sitting in the body plethysmograph:

$\int \dot{V}_B$ = integrated flow signals of the body plethysmograph

$\int \dot{V}_m$ = integrated flow signals at the mouth

P_m = pressure at the mouth

frequency response (Van de Woestijne and Bouhuys, 1969).

To measure the vital capacity and its components (tidal volume, inspiratory reserve volume and expiratory reserve volume) the patient was seated in the body plethysmograph, breathing through the mouth pneumotachograph with a mouthpiece and a clip on her nose. The volume changes at the mouth were plotted against time on the X-Y recorder. The recorder was calibrated using a one litre syringe.

For measuring the functional residual capacity (FRC) the patient was seated in the closed body plethysmograph and again using a mouthpiece and nose clip, she was instructed to breath quietly. A shutter, which could be operated by remote control to block off the mouthpiece, was activated at the end of a normal expiration. The patient then inspired against the closed shutter and the pressure changes at the mouth (Pm) were measured by a pressure transducer. This pressure is equal to the alveolar pressure when the airway is closed by the shutter and there is effectively no flow.

The changes before and during closure of the shutter were plotted on an X-Y recorder, the volume changes of the body plethysmograph (V_B) being plotted on the X-axis and the pressure changes in the mouth (Pm) on the Y-axis.

As a result of the measurement (i.e. application of the shutter while breathing quietly), a slope is generated on the X-Y recorder, as shown in Figure 18. From this slope the angle θ was drawn, where:

$$\text{Tan } \theta = \frac{b}{a}$$

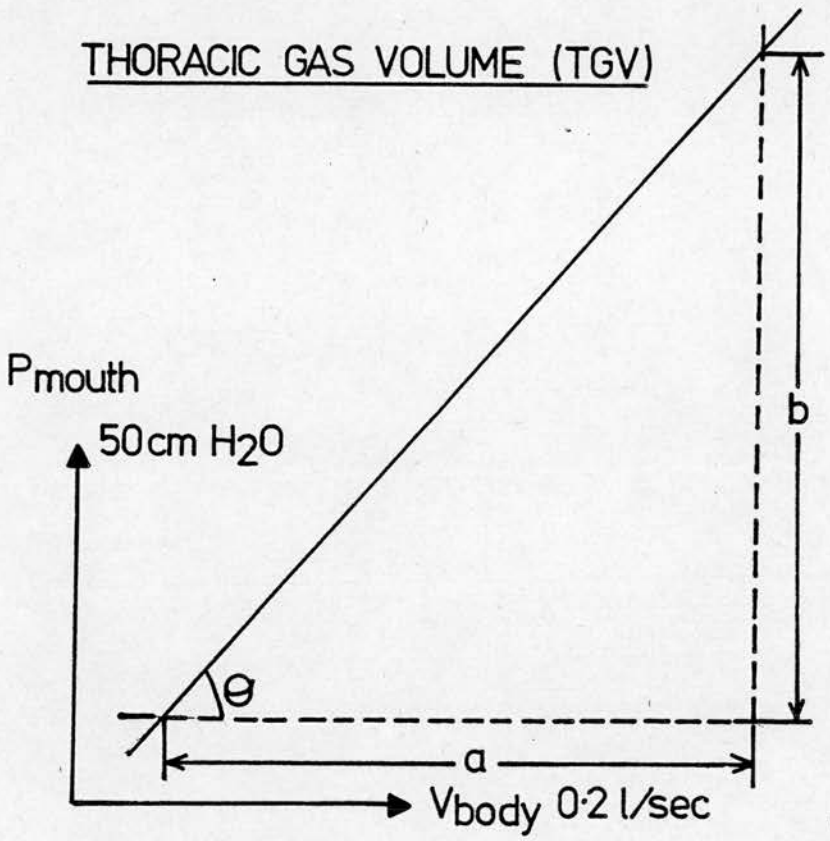


Figure 18

The slope generated on the X-Y recorder as a result of application of the shutter while breathing quietly, where b corresponds to changes in mouth pressure (P_m) and a corresponds to changes in plethysmographic volume (V_B).

The use of the body plethysmograph to measure the thoracic gas volume was described by Dubois, Botelho, Bedell, Marshal and Comroe (1956). Boyles Law states that at a constant temperature, the product of pressure and volume for a given mass of any gas is constant, i.e. PV = constant --- (1). If the P and V changes by ΔP and $-\Delta V$ respectively, then:

$$(P + \Delta P).(V - \Delta V) = PV \text{ --- } (2)$$

This relationship is simplified to:

$$V = P.\ \frac{\Delta V}{\Delta P} \text{ --- } (3)$$

where P = alveolar dry gas pressure which is equal to barometric pressure - water pressure in the lung = P_B - 47 mm Hg.

V = Thoracic gas volume

ΔV = Changes in the volume due to compression of the chest by respiratory muscle when the airways are obstructed by the shutter.

ΔP = Changes in alveolar pressure when breathing against the shutter.

Thus $V = (P_B - 47).\ \frac{\Delta V}{\Delta P}$ --- (4)

at this point V in mls

P_B - 47 in mm Hg

ΔV in mls

ΔP in mm Hg

According to the range used, which was recommended by the manufacturers, the calibration of 20 mls air = 10 mm displacement of the X-Y recorder. Thus, ΔV = a mm x $\frac{20}{10}$ = a x 2 ml. Also the calibration of 25 cms H_2O = 50 mm

displacement and to change that to mmHg, $\frac{25}{1.36}$ mm Hg = 50 mm.

Thus $\Delta P = b \times \frac{25}{1.36 \times 50}$

$$= \frac{b}{2.72}$$

Therefore $V = (P_B - 47) \times 2 \times a \div \frac{b}{2.72}$ --- (5)

$$= (P_B - 47) \times 2 \times 2.72 \times \frac{a}{b}$$

$$= 5.44 \times \frac{a}{b} \times (P_B - 47) \quad \text{--- (6)}$$

The dead space between the mouthpiece and the pneumotachograph is subtracted, this being measured by water displacement and found to be 140 mls. Thus, to get the VTG (Thoracic gas volume) or FRC (Functional residual capacity), the following formula was applied:

$$\text{VTG (in mls)} = 5.44 \times \frac{a}{b} (P_B - 47) - 140 \quad \text{--- (7)}$$

3. Airway resistance (AWR) and specific airway conductance (sGaw)

For these measurements the patient was seated in the closed body plethysmograph and was instructed to pant at the frequency of a metronome of about 1.0 breath/second for five seconds. During the first part of the measurement the patient rebreathed through a heated pneumotachograph, connected to a plastic bag inside the body plethysmograph, the bag being filled with humidified air at a temperature of 37°C. The patient then panted against a closed shutter

at the same frequency (according to the method of Dubois, Botelho and Comroe, 1956).

During each measurement the results were plotted on the X-Y recorder. In the first manoeuvre (with the shutter open), the flow signals at the mouth ($\dot{V}_m$) were plotted on the Y-axis against the volume signals of the body plethysmograph (V_B) on the X-axis, giving a loop, as shown in Figure 19. A line was drawn between the points on the loop corresponding to the flows of zero and 0.5 litre/second during inspiration (Cotes, 1975) and the slope $\frac{d}{c}$ of this line was measured.

Using equation --- (3)

$$\Delta V = \frac{V}{P} \cdot \Delta P \quad \text{--- (8)}$$

Dividing both sides of the equation by $\dot{V}$ (flow)

$$\frac{\Delta V}{\dot{V}} = \frac{V}{P} \cdot \frac{\Delta P}{\dot{V}} \quad \text{--- (9)}$$

Hence:

$$\frac{\Delta P}{\dot{V}_m} = \frac{\Delta V}{\dot{V}_m} \cdot \frac{P_B - 47}{V} \quad \text{--- (10)}$$

Where ΔP = The pressure difference between the alveoli and P_B (mm Hg)

ΔV = Changes in the chest volume caused by ΔP (ml)

$P_B - 47$ = Dry gas pressure (mm Hg)

V = Thoracic gas volume (ml)

$\dot{V}_m$ = Flow at the mouth (litre/second)

i.e. $$\text{Resistance} = \frac{\Delta V}{\dot{V}_m} \times \frac{P_B - 47}{V} \text{ (mm Hg/L/sec)} \quad \text{--- (11)}$$

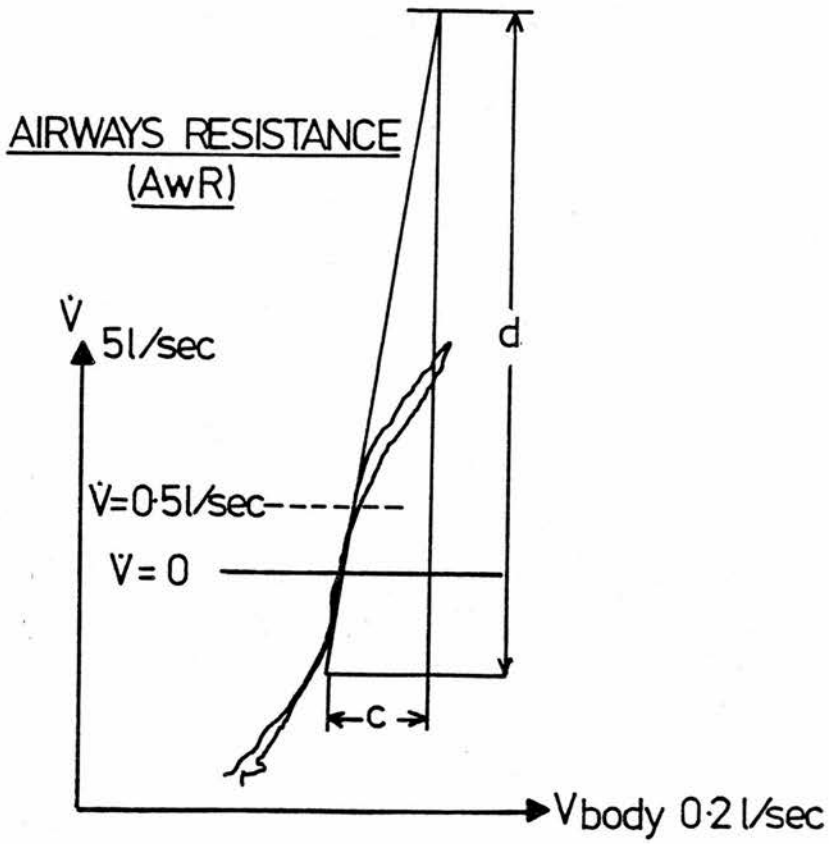


Figure 19

The loop generated on the X-Y recorder as a result of panting with the shutter open, where d corresponds to changes in flow at the mouth ($\dot{V}m$) and c corresponds to changes in plethysmographic volume (V_B).

$\frac{\Delta V}{\dot{V}_m}$ was obtained from the slope in the first measurement (i.e. panting with the shutter open); whereas

$\frac{P_B}{V}$ was calculated from the slope in the second measurement (i.e. panting against the closed shutter) which = $\frac{\Delta P}{\Delta V}$

$(P_B - 47)$ mm Hg = $(P_B - 47) \times 1.36$ cm H_2O

Therefore,

$$\text{Resistance (R)} = \frac{\Delta V}{\dot{V}_m} \times \frac{(P_B - 47) \times 1.36}{VTG} \text{ cm}H_2O/L/\text{sec} \quad \text{--- (12)}$$

For the settings used in this measurement, the calibrations were 0.5 L/sec = 10 mm displacement (i.e. $\dot{V}_m$ = d (mm) . $\frac{0.5}{10}$) and 20 ml of air = 10 mm displacement (i.e. ΔV = c (mm) . $\frac{20}{10}$)

Therefore,

$$R = \frac{c \times 2}{d/20} \times \frac{1.36\ (P_B - 47)}{VTG} \text{ cm}H_2O/L/\text{sec} \quad \text{--- (13)}$$

According to the manufacturers, the mechanical resistance of the system is 0.25 cmH_2O/L/sec and this should be deducted from the airway resistance which was calculated from equation --- (13). Thus, the correct formulae which was used to calculate the airway resistance (AWR) is:

$$AWR = 54.4 \times \frac{c}{d} \times \frac{(P_B - 47)}{VTG} - 0.25 \text{ cm}H_2O/L/\text{sec} \quad \text{--- (14)}$$

The results were expressed as conductance (i.e. reciprocal of resistance) per litre of thoracic gas volume, and the index obtained was the specific conductance (sGaw):

$$sGaw = \frac{1/AWR}{VTG\ (L)} = \frac{c}{VTG\ (L)} \quad \text{cm}H_2O^{-1}.\text{sec}^{-1}$$

The relationship between airway resistance (AWR) and thoracic gas volume (VTG) for a normal subject is a rectangular hyperbola (i.e. the resistance varies inversely with the volume of the gas in the thorax at the time of the measurement); whereas the airway conductance (Gaw) is assumed to be directly proportional to the thoracic gas volume (VTG) (Brisco and Dubois, 1958). Thus, on that assumption, airway conductance (Gaw) had been standardized for the thoracic gas volume (VTG) changes by using the index specific conductance (sGaw), which is equal to Gaw/VTG (Guyatt, Alpers, Hill and Bramley, 1967).

4. Flow volume curves

The flow volume curve describes the relationship of the maximal flow rate to the intrathoracic gas volume during forced expiration (Figure 20).

The flow volume curves were obtained using the body plethysmograph to measure the changes in the lung volume (V_B) during maximal expiration from total lung capacity; whereas the flow rate ($\dot{V}_m$) was obtained by differentiating the volume signals through a fast response spirometer (Ohio) which was connected to the mouthpiece. Both these signals were fed into an on-line PDP 11/40 computer for direct calculation of the maximal flow at 50% vital capacity ($\dot{V}_{max}$ 50) and at 30% vital capacity ($\dot{V}_{max}$ 30). These measurements were repeated at least three times and the greatest values for $\dot{V}_{max}$ 50 and $\dot{V}_{max}$ 30 were taken. The variations in the forced vital capacities (FVC) over these three measurements were always less than 5%.

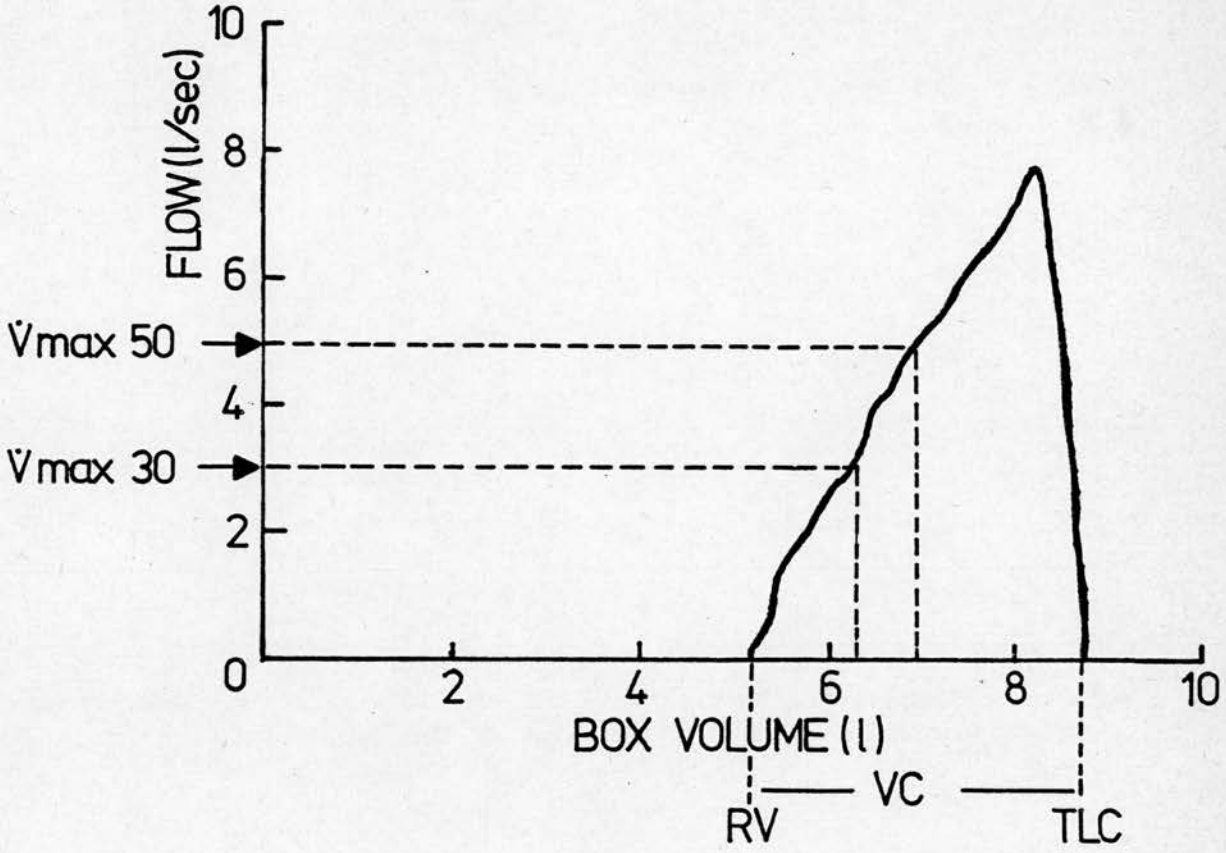


Figure 20

The flow volume curve, as drawn following maximal forced expiration. The X-axis shows the changes in plethysmographic volume and the Y-axis shows the flow changes ($\dot{V}m$).

The maximum expiratory flow rate in these measurements (when made in a body plethysmograph), breathing air, depends primarily on three factors: Firstly, the elastic recoil pressure of the lung (Pst) which is important throughout the whole vital capacity (VC) range, as the effective driving pressure producing the maximum expiratory flow rate (MEFR). Secondly, the cross-sectional area of large airways which is important at high lung volumes. Thirdly, the frictional resistance of small airways (R) which is important at low lung volumes (Macklem and Mead, 1967). Furthermore, Hyatt, Schilder and Fry (1950) demonstrated that the relationship between the maximal expiratory flow and the degree of lung inflation was effort-dependent over the upper half of the vital capacity. However, over the lower half of the vital capacity, that relationship was independent of effort, uninfluenced by the addition of external resistances and highly reproducible.

Thus, measurements of the maximal flow at 50% vital capacity ($\dot{V}_{max}$ 50) and at 30% vital capacity ($\dot{V}_{max}$ 30) are dependent on the elastic recoil of the lung (Pst) as the total effective driving pressure (which is equal to Palv-Ppl) and on the resistance of the airways between the alveoli and the points when the total pressure drop equal to Pst. These points were termed equal pressure points (EPP), since the pressure at the inner wall of the airways at these points equal to Palv-Pst which is equal to Ppl. The resistance of airways between the alveoli and EPP is referred to as the upstream resistance (Rus), so that

the MEFR = $\frac{Pst}{Rus}$ (Macklem and Mead, 1967).

Therefore measurements of the maximal flow at lower lung volumes were used as an index of the airway resistance at the upstream segments (Rus), i.e. the resistance of the small airways.

5. Measurement of transfer factor for carbon monoxide (T_{CO})

The transfer factor (diffusing capacity) for the lung for carbon monoxide is the rate at which carbon monoxide is absorbed from the alveolar gas in mmol/minute/unit of effective alveolar transfer gradient. This index is a function of both the diffusing capacity of the alveolar capillary membrane and the rate at which carbon monoxide combines with haemoglobin in the alveolar capillaries (Roughton and Forster, 1957).

If T_l is the transfer factor (diffusing capacity) for the lung for carbon monoxide (CO), D_m is the diffusing capacity of alveolar capillary membrane, V_c is the volume of the blood in the alveolar capillaries and θ is the reaction rate of CO with oxy-haemoglobin, then:

$$\frac{1}{T_l} = \frac{1}{D_m} + \frac{1}{\theta V_c}$$ is the relationship between them

The Resparameter (Mk IV), (PK Morgan Ltd) was used for the measurement of transfer factor for CO, using the single breath technique. This method was first described by Marie Krogh at the beginning of this Century, a single deep breath of mixture of CO in air being taken into the

lung. Then, this method was modified by Fowler, who suggested that the inspired gas mixture should contain Helium in addition to CO (Bates and Christie, 1965), to measure the alveolar volume simultaneously, so allowing for varying dilution of the inspired CO and this in alveolar CO pressure.

The patient was seated (with a mouthpiece and a clip on her nose) breathing quietly into the Resparameter. She was then instructed to breath out to residual volume and then inhale a vital capacity breath of the test gas (approximately 0.3% CO, 12% Helium and the remainder air), hold her breath for 10 seconds, then exhale slowly. After exhalation of 700 ml a sample of the alveolar gas was collected for analysis. The procedure is illustrated in Figure 21. The period of effective breath holding started after the first 700 ml of inspiration, until the end of the first 700 ml of expiration, to allow for dead space washout, as given automatically by the resparameter.

Following these measurements the amount of CO in the alveolar gas at the beginning and at the end of breath holding was calculated and the alveolar volume during this time was calculated from the dilution of the Helium in the test breath.

The following formula was used to calculate T_{CO} (single breath):

$$T_{CO} = b \times V_A/t \times \text{Log}_{10} \left[\frac{F_{ICO} \times F_{A\,He}}{F_{IHe} \times F_{ACO}}\right] \quad \text{mmol/min/kPa}$$

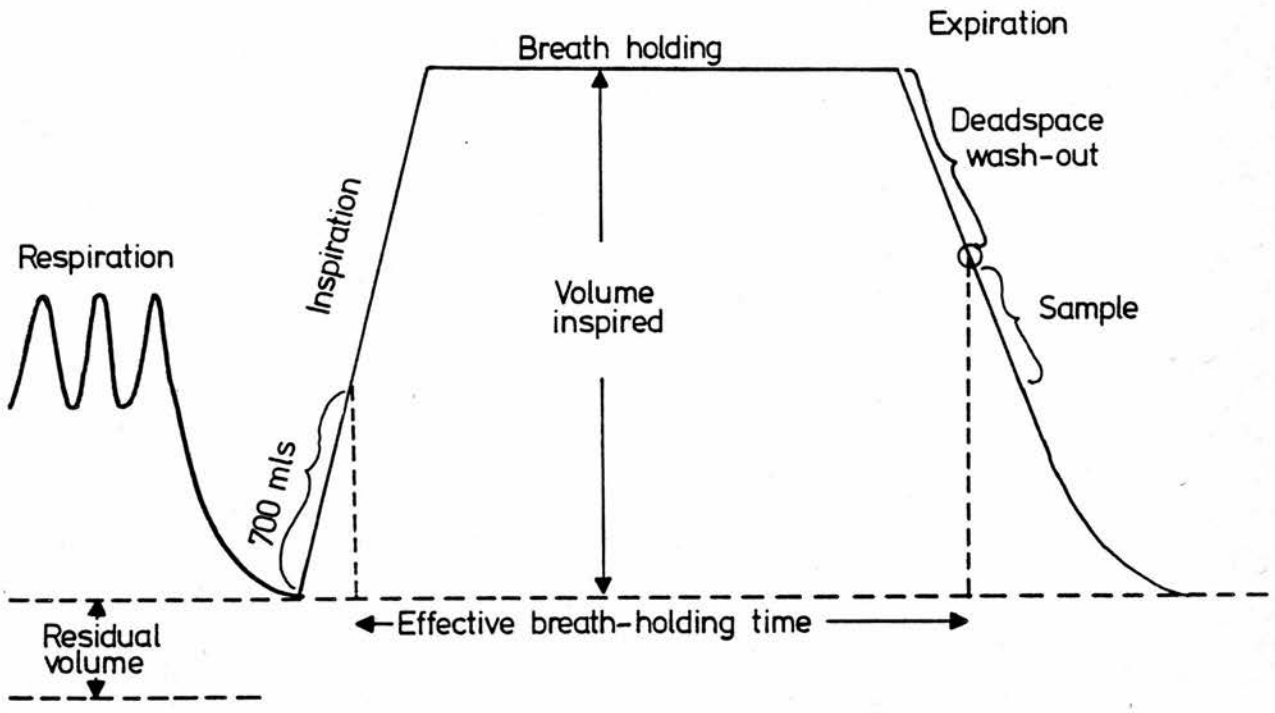


Figure 21

This illustrates the procedure used in the measurements of T_{CO}.

Where V_A = alveolar volume in ml BTPS

t = the time of effective breath holding in seconds

F_{ICO} = concentration of CO in inspired gas

F_{ACO} = concentration of CO in alveolar gas at the end of the breath hold

F_{IHe} = concentration of Helium in inspired gas

F_{AHe} = concentration of Helium in alveolar gas

b = 53.6 = constant

Where the alveolar concentration of carbon monoxide at time zero is:

$$(F_{OA\ CO}) = F_{ICO} \times \frac{F_{A\ He}}{F_{I\ He}}$$ (as derived by Cotes, 1975)

Alveolar effective volume $V_A = (V_I \times \frac{F_{I\ He}}{F_{A\ He}})$ litres BTPS

Where V_I = volume of gas inspired in litres BTPS

$F_{I\ He}$ and $F_{A\ He}$ = Helium concentration in the inspired and expired alveolar gas

For calculation of the predicted values, the following formula is applied for females:

$$T_{CO}\ (mmol/min/kPa) = [(height \times 6.87) - (age \times 0.017) - 1.83] \pm 1.44\ (S.D.)$$

(Cotes and Hall, 1970)

Accuracy of measurements

1. Calibration

Each instrument used for these measurements was calibrated as below. The vitalograph which is a dry spirometer was calibrated by water displacement, as shown

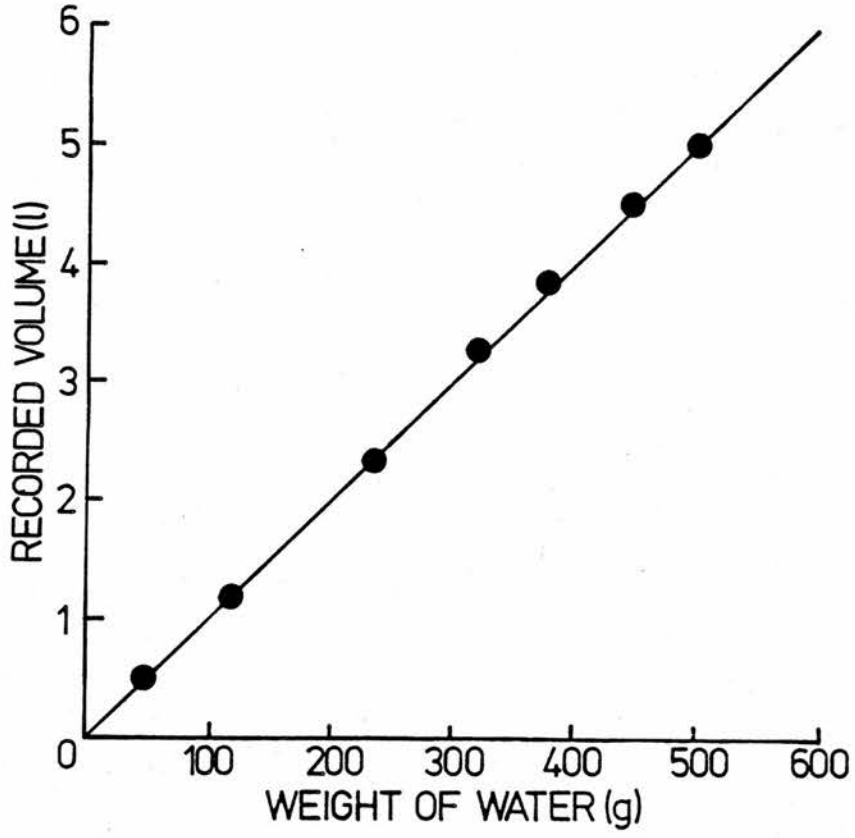


Figure 22

The calibration of the vitalograph by water displacement. The X-axis shows the weight of the water in gms and the Y-axis indicates the recorder volume in litres.

in Figure 22. Also, the spirometer of the P.K. Morgan Resparameter (for measuring T_{CO}) was calibrated by water displacement; whereas the carbon monoxide and Helium analyser was calibrated using different dilutions of Helium and carbon monoxide, as shown in Figure 23 and Figure 24. On the other hand, the mouth pressure (Pm) transducer of the body plethysmograph was calibrated and checked periodically against a water manometer. Moreover, the volume signals at the mouth were calibrated daily using a one litre syringe. The fast response spirometer volume signals were calibrated using a one litre syringe. The body plethysmograph/computer system was calibrated daily by introducing volume signals, using an accurate one litre syringe (previously calibrated by water displacement); the flow was calibrated by an electrical signal which had previously been calibrated against a rotameter. Thereafter a more accurate absolute flow calibration was obtained through a slow expiration manoeuvre made by a subject (with normal airway resistance) in the body plethysmograph. Thus, the integrated flow signals at the mouth ($\int \dot{V}_m$) and the volume signals of the body plethysmograph (V_{box}) are recorded, compared and equalized by the computer (i.e. $\int \dot{V}_{mouth} = V_{box}$). The slow expiration manoeuvre is made to minimize gas compression.

2. Reproducibility

Lung volumes, airway resistance and flow volume curves were measured in five normal women aged 20-28 years,

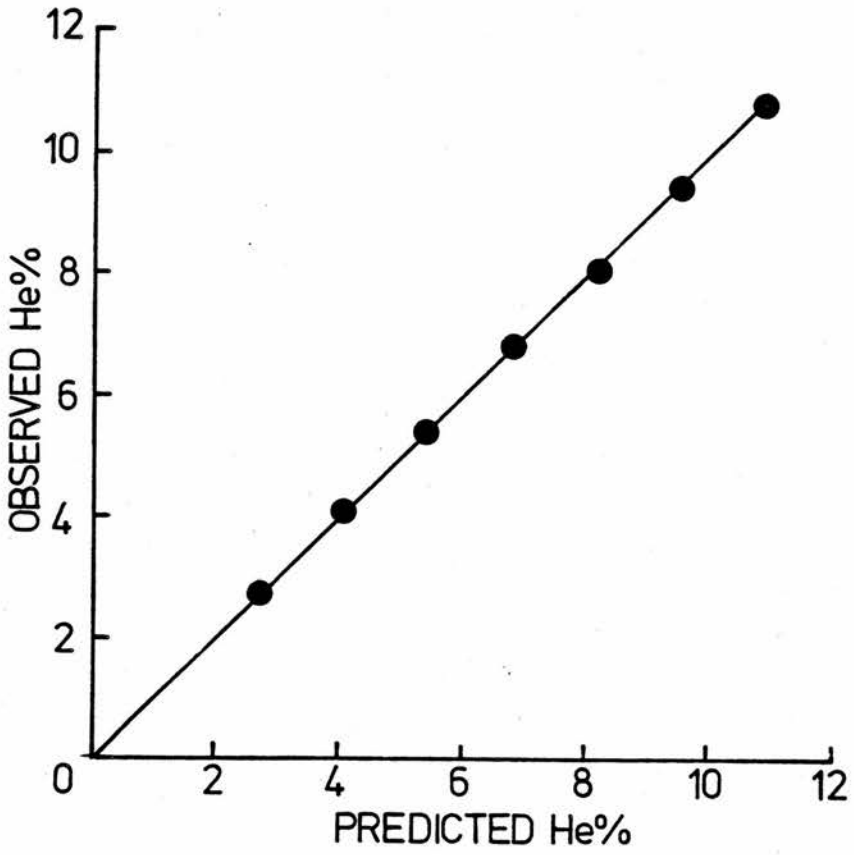


Figure 23

The calibration of Helium analyser, with different dilutions of Helium. The X-axis indicates the predicted Helium percentage and the Y-axis shows the observed Helium percentage.

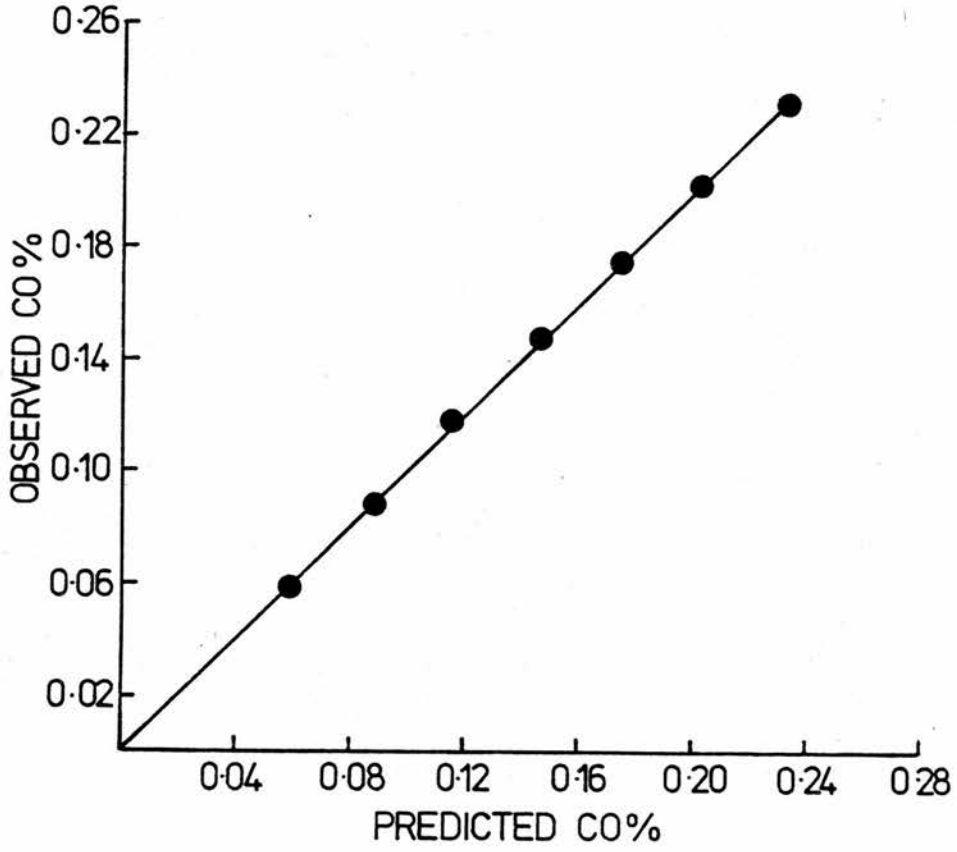


Figure 24

The calibration of carbon monoxide analyser, with different dilutions of carbon monoxide. The X-axis shows the predicted CO percentage and the Y-axis shows the observed CO percentage.

staff in the department.

The lung volumes and airway resistance measurements were repeated for each subject on five different occasions, over a period of 10 weeks. The mean and standard deviation for each subject of the total lung capacity (TLC), residual volume (RV), thoracic gas volume (VTG) and specific airway conductance (sGaw) are shown in text Table 2a. The coefficient of variation for these measurements are shown in text Table 3, which show values from 11.4% for RV, 2.44% for TLC, 2.05% for VC, 1.88% for VTG and 3.13% for sGaw.

The flow volume curve measurements were also repeated for each subject on 5 different occasions over a period of two weeks. The mean and standard deviations of forced expiratory volume at 1.0 second (FEV_1), $\dot{V}_{max}$ 50 and $\dot{V}_{max}$ 30 for each subject are shown in text Table 2b. The coefficient of variation for these measurements are also shown in text Table 3, which shows values of 2.37% for FEV_1, 3.55% for $\dot{V}_{max}$ 50 and 4.88% for $\dot{V}_{max}$ 30.

The transfer factor for carbon monoxide (T_{CO}) was measured in 5 normal women (staff of the department) and the measurement was repeated on 5 different occasions over a period of 2-8 weeks. The means and standard deviations for each subject are shown in text Table 4, together with their coefficient of variation.

As shown, the reproducibility of these measurements was adequate.

TEXT TABLE 2a

Reproducibility of Lung Volume Measurements (TLC, RV, VC, VTG) & Specific Conductance (sGaw) in 5 Normal Women (Mean ± S.D.)

Subject	TLC (litres)	RV (litres)	VC (litres)	VTG (litres)	sGaw (sec.-1kPa-1)
L Mc	4.83 ± 0.16	1.41 ± 0.10	3.42 ± 0.10	3.49 ± 0.14	1.831 ± 0.156
P K	3.65 ± 0.07	0.54 ± 0.05	3.11 ± 0.04	2.72 ± 0.03	1.904 ± 0.051
P M	4.17 ± 0.09	0.68 ± 0.12	3.50 ± 0.07	3.18 ± 0.07	1.940 ± 0.022
C O	4.02 ± 0.08	0.64 ± 0.07	3.38 ± 0.06	2.81 ± 0.03	2.189 ± 0.035
F T	5.64 ± 0.16	0.81 ± 0.10	4.83 ± 0.11	3.89 ± 0.04	1.609 ± 0.028

TEXT TABLE 2b

Reproducibility of Flow Volume Curves (FEV_1, $\dot{V}_{max}$ 50 and $\dot{V}_{max}$ 30 in 5 Normal Women (Mean ± S.D.)

Subject	FEV_1 (litres)	$\dot{V}_{max}$ 50 (L/sec)	$\dot{V}_{max}$ 30 (L/sec)
L Mc	3.60 ± 0.10	4.86 ± 0.17	3.04 ± 0.32
P K	2.83 ± 0.05	3.04 ± 0.10	2.32 ± 0.07
C O	3.02 ± 0.09	3.63 ± 0.20	2.10 ± 0.08
M L	3.64 ± 0.07	4.29 ± 0.13	2.37 ± 0.07
J B	3.73 ± 0.09	5.75 ± 0.14	3.19 ± 0.13

TEXT TABLE 3

Coefficent of Variation (%) of the Measurements in the Normal Individuals

Subject	TLC (%)	RV (%)	VC (%)	VTG (%)	sGaw %	FEV_1 %	$\dot{V}_{max}$ 50 (%)	$\dot{V}_{max}$ 30 (%)
L Mc	3.31	7.09	2.92	4.01	8.52	2.78	3.50	10.53
P K	1.92	9.26	1.29	1.10	2.68	1.77	3.29	3.02
C O	1.99	10.94	1.78	1.07	1.60	2.98	5.51	3.81
P M	2.16	17.65	2.00	2.20	1.13			
F T	2.84	12.35	2.28	1.03	1.74			
J B						2.41	2.44	4.08
M L						1.92	3.03	2.95
Mean Coefficient	2.44	11.46	2.05	1.88	3.13	2.37	3.55	4.88

TEXT TABLE 4

Reproducibility of Transfer Factor Measurements (TC_O) & Coefficient of Variation in 5 Normal Subjects (Mean ± S.D.)

Subject	TC_O (mmol/min/kPa)	Coefficient of variation (%)
I	7.04 ± 0.185	2.63
II	6.88 ± 0.073	1.06
III	8.16 ± 0.052	0.64
IV	7.95 ± 0.177	2.23
V	7.08 ± 0.266	3.76
Mean	7.42 ± 0.151	2.06

3. Linearity of the measurements

The linearity of the body plethysmograph flow meters (i.e. the mouth pneumotachograph and the "box" pneumotachograph) were tested using a one litre syringe which slowly pumped air into the closed body plethysmograph via the external orifice of the mouth flow meter and out through the "box" flow meter. The integrated volume changes and integrated "box" volume changes were plotted on an X-Y recorder. These volume displacements were linear up to 10 litres, as shown in Figure 25.

The linearity of the Ohio spirometer was tested using also a one litre syringe connected to a three-way tap. Air was slowly pumped into the spirometer and the output signal recorded against time on an ink jet recorder (Minograph). The volume displacements were linear up to 10 litres, as shown in Figure 25.

For transfer factor (T_{CO}) measurements, the spirometer volume was calibrated by water displacement and found to be accurate up to 7 litres. The analyser readings for Helium and carbon monoxide were found to be linear in the range of (0.00 - 14%) for Helium and in the range of (0.00 - 0.30%) for carbon monoxide, on using serial dilutions of Helium and carbon monoxide mixtures made by a precision mixing pump (Wosthoff).

4. Dynamic response study

To test the frequency response of the body plethysmograph flow meters and the Ohio spirometer, a modified 500 cc motor cycle engine which had a measured stroke volume of

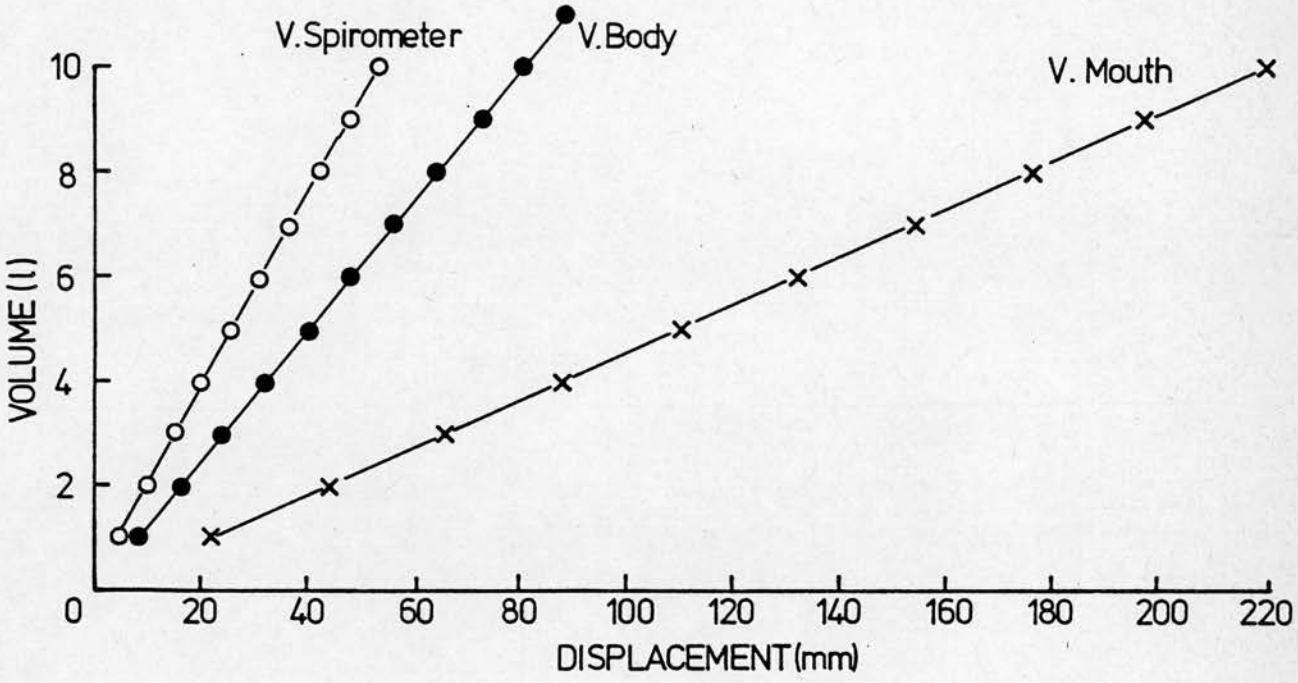


Figure 25

Linearity of the plethysmograph flow meters and the Ohio spirometer. The integrated flow change (volume) displacements in mm (X-axis), plotted against volume changes in litres for each parameter.

500 ml was available. This engine, used as a constant amplitude oscillating pump, was driven at frequencies from 0.5 Hz up to 12 Hz by an electric motor.

The output of the pump was introduced into the closed body plethysmograph via the external orifice of the mouth flow meter, the plethysmograph venting to air via the "box" flow meter, as illustrated in Figure 26.

The amplitudes of the sinusoidal waves from the mouth flow meter and the "box" flow meter were plotted against frequency as a percentage of the amplitude at 0.5 Hz. As shown in Figure 27 the amplitude responses of the mouth flow meter and the "box" flow meter were adequate from 0.5 Hz up to 8.0 Hz, which is adequate as the patients were panting at a rate of approximately 1.0 Hz for the airway resistance measurements and at about 0.3 Hz for the lung volume measurements.

The output of the pump was also introduced into the Ohio spirometer via the mouth flow meter. The amplitudes of the sinusoidal waves from the Ohio spirometer was plotted against frequency as a percentage of the amplitude at 0.5 Hz, as shown in Figure 27. The amplitude response of the Ohio spirometer was flat from 0.5 Hz to 6.0 Hz, which was considered adequate for the measurements of $\dot{V}_{max}$ 50 and $\dot{V}_{max}$ 30. These responses were considered adequate for these measurements (McCall, Hyatt, Noble and Fry, 1957).

The phase differences in degrees (1 cycle = 360 degrees) between the mouth flow meter and the "box" flow meter and

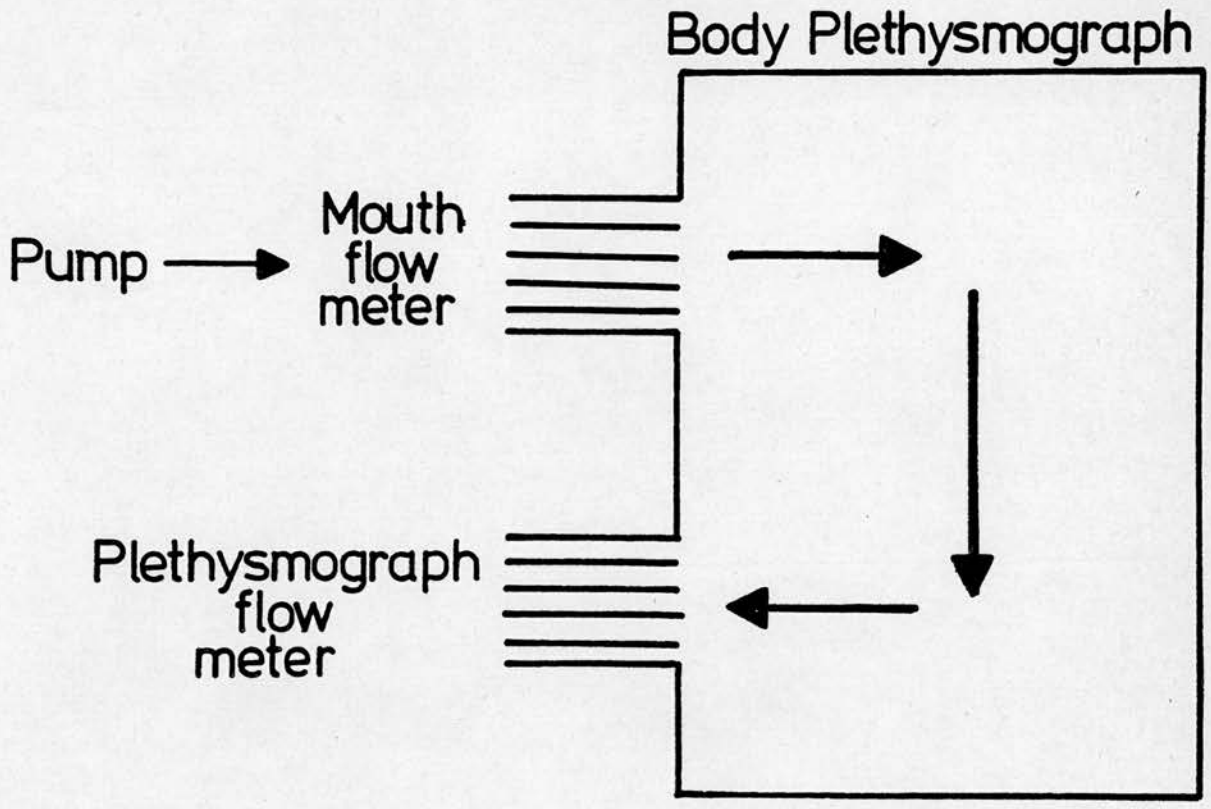


Figure 26

Testing the frequency response of the body plethysmograph flow meters. The motor cycle engine pumps into the plethysmograph via the mouth flow meter and the body plethysmograph venting air via the "box" flow meter.

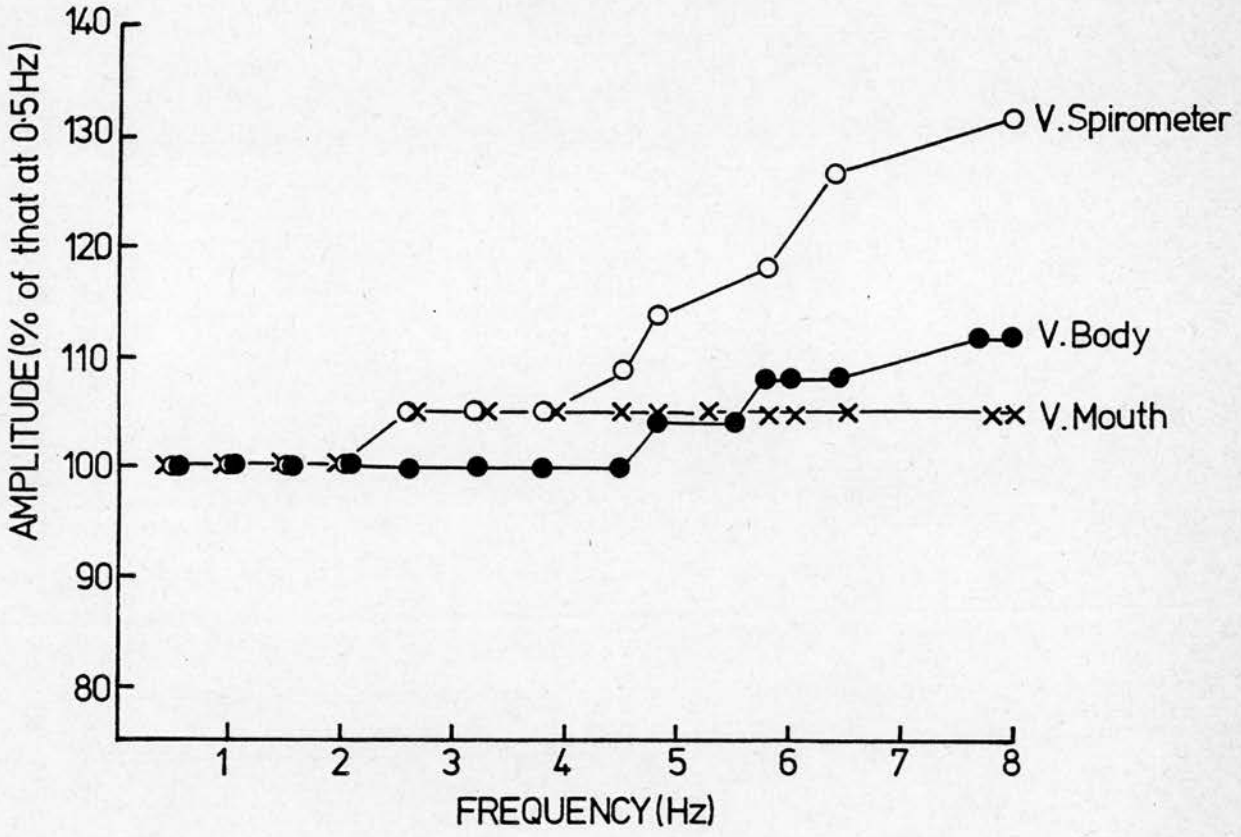


Figure 27

The frequency response (X-axis) of the amplitude of the sinusoidal waves (drawn as percentage of that at 0.5 Hz), of the plethysmograph flow meters and the Ohio spirometer.

between the mouth flow meter and the Ohio spirometer were plotted against frequency (Figure 28). There was negligible phase lag from a frequency of 0.5 Hz up to 8.0 Hz in the former, and up to 11 Hz in the latter.

iii) Regional lung function measurements

The regional distribution of ventilation and perfusion in the lung was studied using the technique of Ball, Stewart, Newsham and Bates (1962), which allowed for quantitative measurements based upon relating both ventilation and perfusion to regional lung volume, as described in detail by Milic-Emili, Henderson, Dolovich, Trop and Kaneko (1966), and Anthonisen and Milic-Emili (1966) giving the regional pulmonary ventilation/unit alveolus ($\dot{V}/E$) and the regional pulmonary perfusion/unit alveolus ($\dot{Q}/E$).

1. Technique

In this study the patient was seated upright on a chair with her back to the gamma camera (Nuclear Enterprises Scinticamera V), breathing around functional residual capacity (FRC) through a mouthpiece (with noseclip), connected to a closed circuit spirometer containing room air. The patient was positioned so that the total lung at maximal inspiration was within the gamma camera field of view. To maintain the patient's position, two centre spots from electric light beams focused on the anterior chest wall were used and an anatomical marker was also used to mark the supra-sternal notch, this producing a "hot spot" on the gamma camera field.

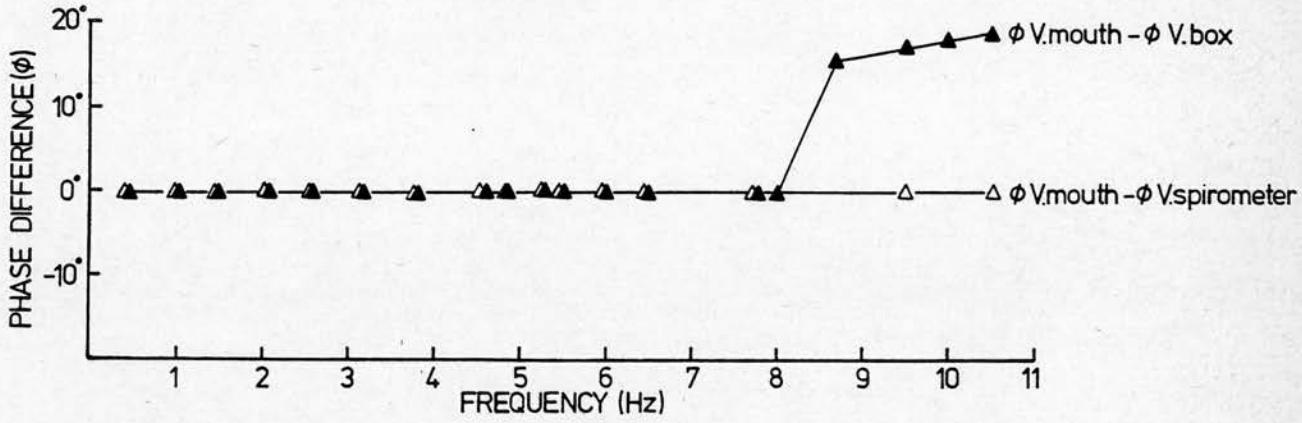


Figure 28

The frequency response (X-axis), plotted against the phase difference (Ø) in degrees between the sinusoidal waves of the mouth flow meter and those of the "box" flow meter and between the sinusoidal waves of the mouth flow meter and those of the Ohio spirometer.

Thereafter the patient was instructed to breath-hold at FRC while a bolus of 1 mCi of radioactive xenon (Xe^{133}) was administered at the mouth. The patient was then instructed to inspire at a constant flow rate (measured by a flow meter consisting of a mesh screen pneumotachygraph connected to a micro manometer) to total lung capacity (TLC) and then to hold the breath for 10 seconds (Figure 29) whilst the regional count rates (disintegration/sec) were recorded, either directly into a computer (PDP 11/34) or onto videotape (Nivico JVC) for subsequent replay into an off-line (PDP 12) digital computer. The patient was then instructed to expire to FRC and then to rebreath quietly through the closed circuit spirometer until equilibration was achieved, as indicated by a constant unchanging count rate from each region. Once again the patient's position was checked by the anatomical marker and the patient instructed to inspire (at whatever flow rate she wished) to TLC, and then to hold her breath for 10 seconds whilst the count rates from each region were recorded. The spirometer circuit was then opened to air, to allow studies of the rate of washout of the Xe^{133} and the count rates were also recorded.

In the sequential study, before and at intervals after radiotherapy, the distribution of ventilation was measured at two different inspiratory flow rates, 0.2 L/sec [where the distribution of ventilation is determined mainly by the regional lung compliance (Milic-Emili et al, 1966; Dollfuss, Milic-Emili and Bates, 1967)] and 1.5 L/sec [where ventilation distribution is mainly determined by

REGIONAL DISTRIBUTION OF VENTILATION & PERFUSION

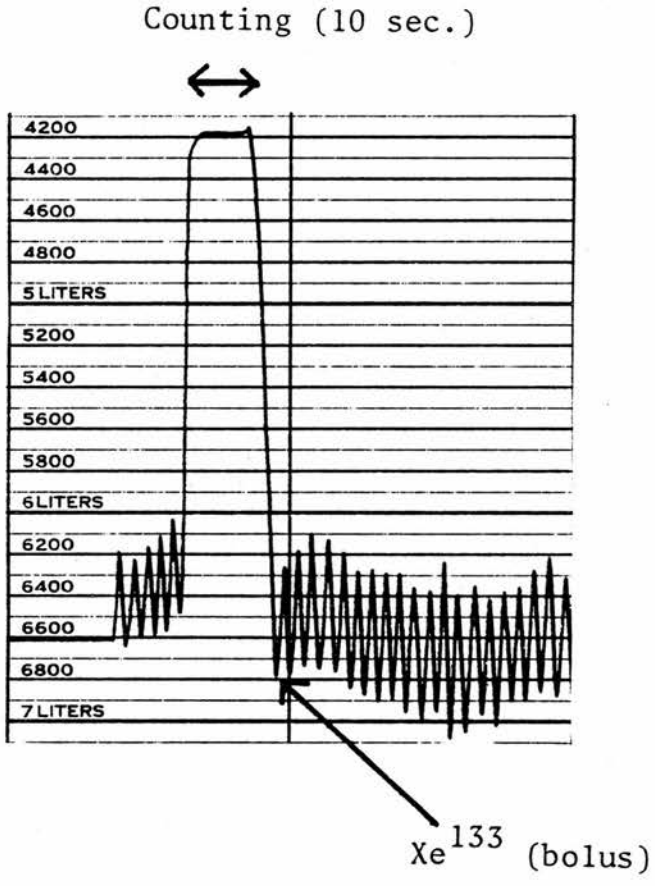


Figure 29

This illustrates the procedure used in the measurements of regional ventilation/perfusion. The Xe^{133} (bolus) given at FRC and breath holds at TLC for 10 seconds, whilst the regional count rates were recorded.

regional resistance (Robertson, Anthonisen and Ross, 1969)]. In the cross-sectional study, at one time after radiotherapy, the ventilation distribution was measured only at an inspiratory flow rate of 0.5 L/sec.

The regional distribution of perfusion ($\dot{Q}/E$) was measured using radioactive xenon (Xe^{133}) in the sequential study, this being injected intravenously (I.V.) (as a 1 mCi bolus in saline solution) into the arm on that side opposite to the breast which received radiotherapy. The patient was then instructed to inspire to TLC and hold her breath for 10 seconds, whilst the regional count rates were recorded. Thereafter the regional count rates during washout of Xe^{133} delivered to the alveoli by perfusion were also recorded. However, the regional distribution of pulmonary perfusion ($\dot{Q}/E$) for the cross-sectional study was measured using 2 mCi Tc^{99m} labelled macroaggregated albumin, which was injected slowly I.V. into the arm, whilst the patient was lying supine [so as to get a relatively uniform distribution of perfusion throughout the lung, relatively unaffected by the gravitational field (Kaneko, Milic-Emili, Dolovich, Dawson and Bates, 1966)] when breathing quietly for a few minutes. The patient was then positioned sitting upright with her back to the gamma camera as before and instructed to inspire to TLC and to hold her breath for 10 seconds, whilst the regional count rates were recorded.

2. <u>The radionuclide</u>

In this study the radionuclides used were radioactive

xenon (Xe^{133}) and technetium-99m (Tc^{99m}) labelled macroaggregated albumin.

A. Xenon (Xe^{133})

Xe^{133} injections were obtained in sterile isotonic saline solution in a multidose syringe cartridge (as 10 mCi in 10 ml saline - Code XAS.110P) from the Radiochemical Centre, Amersham (RCC). Xe^{133} is chemically and physiologically inert and was used as a radioactive indicator with a half-life of 5.25 days. The energy of gamma-emission is 81 KeV and a dose of 1 mCi injection delivers only 14 mrads to the lungs. Xe^{133} has been used as an indicator for the assessment of rates of perfusion and ventilation/unit lung volume in various regions of the lung (Ball et al, 1962; Milic-Emili et al, 1966; Anthonisen and Milic-Emili, 1966; Dollfuss, Milic-Emili and Bates, 1967; Bake, Wood, Murphy, Macklem and Milic-Emili, 1974; Warren, Warren, Hare and Muir, 1976; Muir, Warren, Warren and Hare, 1975). In this study a dose of 1 mCi of Xe^{133} was withdrawn into a 20 ml syringe containing air and shaken well; then administered as the gaseous form of Xe^{133}, to be inhaled by the patient for the regional ventilation measurements. However, Xe^{133} was administered I.V. to give a 1 mCi dose as a saline solution, for measurement of the regional perfusion. The total dose of Xe^{133} given to the patient was 3 mCi, in the sequential study and 1 mCi in the cross-sectional study.

B. Technetium-99m labelled macroaggregated albumin (MAA) (Tc^{99m})

Tc^{99m} was also obtained from the Radiochemical Centre. The Tc^{99m} sterile generator, which contains molybdenum-99 was absorbed on alumina in a sterilized plastic column, surrounded by lead shielding. The column was eluted aseptically using pressurized vials of sterile saline and emptied into a sterile collection vial. The elute obtained was labelled onto macroaggregated albumin, thus yielding a technetium-99m (Tc^{99m}) labelled suspension suitable for I.V. injection for lung scintigraphy. Tc^{99m} is a transitional metal which decays by isometric transition (half-life 6 hours) to Tc^{99}, with the emission of a gamma ray with an energy of 140 kilo electric volts (KeV) (Castronovo, 1975).

In this study a dose of 2 mCi of Tc^{99m} MAA, containing a minimum of 200,000 particles, was injected I.V. into the arm, whilst the patient was lying supine and breathing quietly for a few minutes. These particles ranged between 10 to 100 μm in diameter. On I.V. injection the majority of these particles are removed from the circulation when first filtered through the pulmonary capillary bed and as these particles, which are thus embolised in the lungs, are labelled with a gamma-emitting radionuclide, this enables the perfusion pattern of the lungs at the time of injection to be observed using the gamma camera (Williams, Lyall, Vernon and Croft, 1974; Bateman and Croft, 1976).

3. The gamma camera

The gamma camera was first described by Anger in 1958. The basic imaging action of the Anger camera consisted of reconstructing the position of light-emitting points in a scintillation crystal from the information contained in sets of current pulses, obtained from photomultiplier tubes, coupled to the crystal (Eichling and Siegel, 1974). Figure 30 shows a schematic diagram of an Anger camera. The action of the camera could be divided into three steps:

1. A light-scintillation image is formed in the scintillation crystal, from the radionuclide distribution in the object, where the gamma photons emitted from the patient pass through the holes of the collimator to reach the scintillation crystal.

2. Conversion of the light scintillations into photomultiplier pulses (the light being transmitted to the hexagonal array of 37 photomultiplier tubes, where the pulses are multiplied in the phototubes).

3. Conversion of these pulses into voltages proportional to positional co-ordinates, by using these multiplied pulses as input to a ratio circuit which determines the location of the scintillation within the crystal and subsequently causes a flash to occur on a cathod-ray oscilloscope display in the appropriate position.

(Eichling and Siegel, 1974).

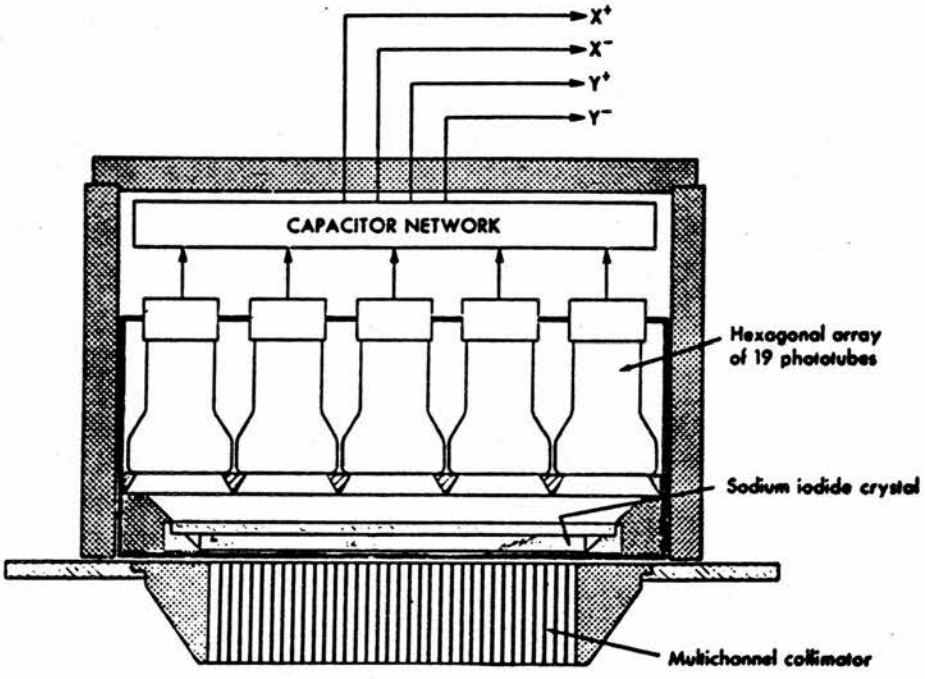


Figure 30

A schematic diagram of a scintillation gamma camera with the multi-channel collimator. (After Eichling and Siegel, 1974).

In this study a Nuclear Enterprises Mk 5 HR gamma camera was used, with a standard field of view of 25 cm diameter so that to view both lungs simultaneously, a high sensitivity diverging collimator (NE 8926) (which has about 15,000 holes in 25 cm diameter face) was necessary. The energy window was preset at 25% and the analyser of the gamma camera was set at 80 KeV for Xe^{133} and 140 KeV for Tc^{99m} MAA studies.

Estimate of errors involved

1. The uniformity of the gamma camera was checked at weekly intervals and was always maintained within ± 15%, being measured within a field size of 250 mm diameter, using a test cell size of 10 mm or smaller and expressing the results by the following formula:

$$\frac{(\text{maximum cell} - \text{minimum cell})}{(\text{maximum cell} + \text{minimum cell})} \times 100$$ (Hannan and Hare, 1976

Although the uniformity of the camera was used ± 15%, this affects all the derived variables that were measured [i.e. ventilation ($\dot{V}$), equilibration (E) and perfusion ($\dot{Q}$)] equally. Thus, on taking ratios of ($\dot{V}/E$) and ($\dot{Q}/E$) this uniformity difference will tend to be cancelled out, if the uniformity variation remains constant over the time for which these measurements were made.

2. The system resolution at 10 cm depth in tissue was 28 mm (full width at half height). The resolution for the high sensitivity diverging collimator

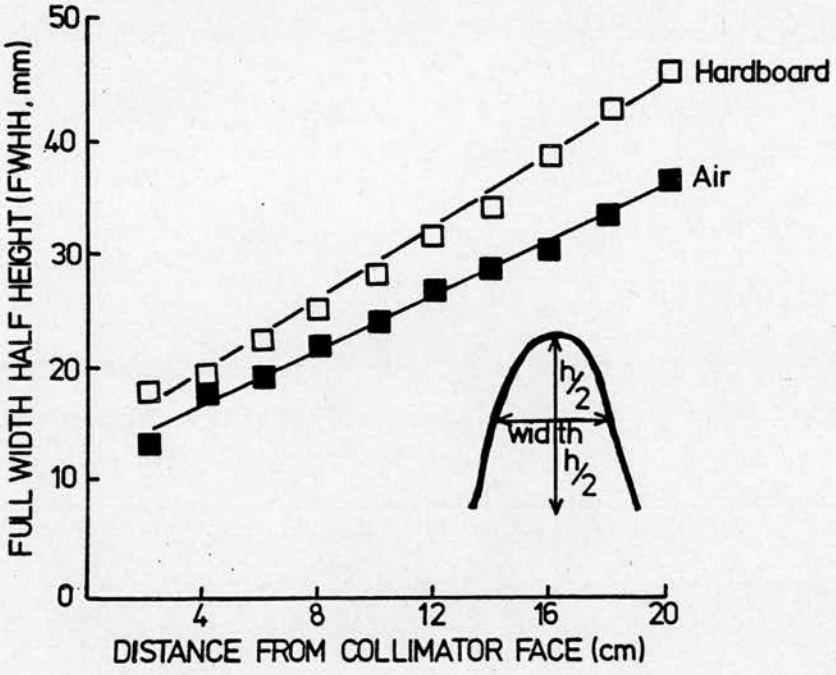


Figure 31

Illustrates the system resolution measurements for high sensitivity diverging collimator in air and in tissue equivalent material (hardboard), as measured using the full width half the height of an 0.5 mm line source of Tc^{99m} positioned along with X or Y axis at different distances from the collimator surface. (After Hannan and Hare, 1976).

in air and in tissue equivalent material is shown in Figure 31, as measured using an 0.5 mm line source of Tc^{99m} being positioned along the X or Y axis at different distances from the collimator surface (Hannan and Hare, 1976).

3. The linearity of the gamma camera was measured using several Tc^{99m} line sources which were positioned 3 cm apart along the X or Y axis and their profiles measured on a multi-channel analyser (Laben 4096). Figure 32 shows the graph of line position versus channel number and indicates a linearity within $\pm$ 3 mm (Hannan and Hare, 1976).

4. The count rate. The observed count rate at different true count rates is shown in Figure 33. The true count rates were measured by two different methods. Firstly, by extrapolating the straight line part of a count rate versus activity graph. Secondly, by plotting the count rate from a Tc^{99m} source on a log scale against time on a linear scale, and extrapolating the straight line portion ($T_{\frac{1}{2}}$ = 6 hours) of the graph. Good agreement was found between the two methods (Hannan and Hare, 1976).

5. The system sensitivity was measured using a 10 cm x 10 cm source of Tc^{99m}. The sensitivity was found to be 16380 counts.sec^{-1}.mCi^{-1}, when using the high sensitivity diverging collimator (NE 8926), which indicates high sensitivity (Hannan and Hare, 1976).

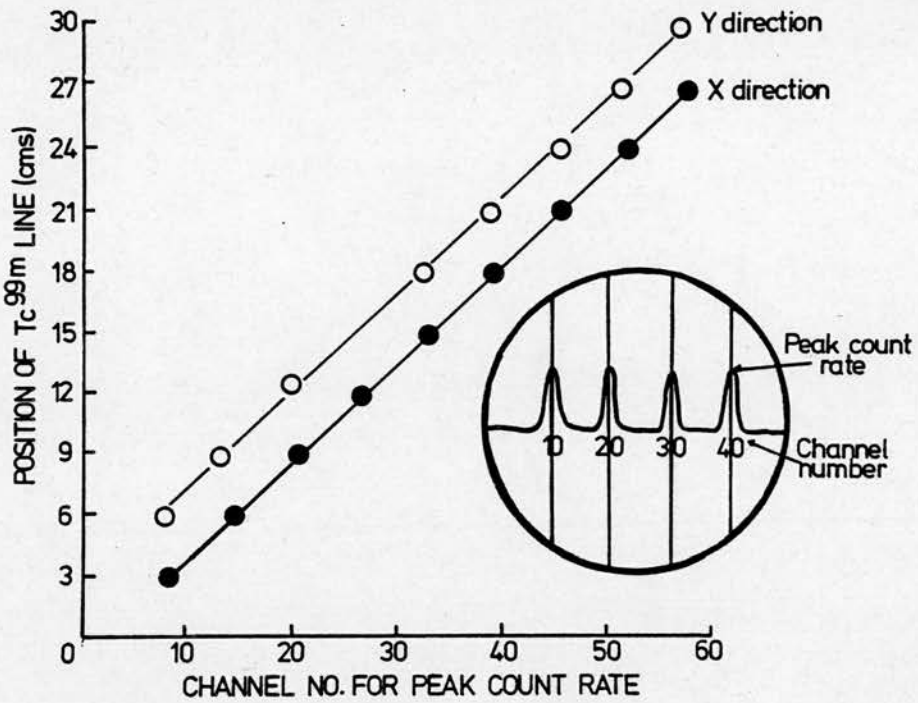


Figure 32

Illustrates measurements of the linearity of the gamma camera using several Tc^{99m} line sources, positioned 3 cm apart along the X or Y axis and their profile measured with the multi-channel analyser. The line position versus the channel number is illustrated and shows linearity within $\pm$ 3 mm. (After Hannan and Hare, 1976).

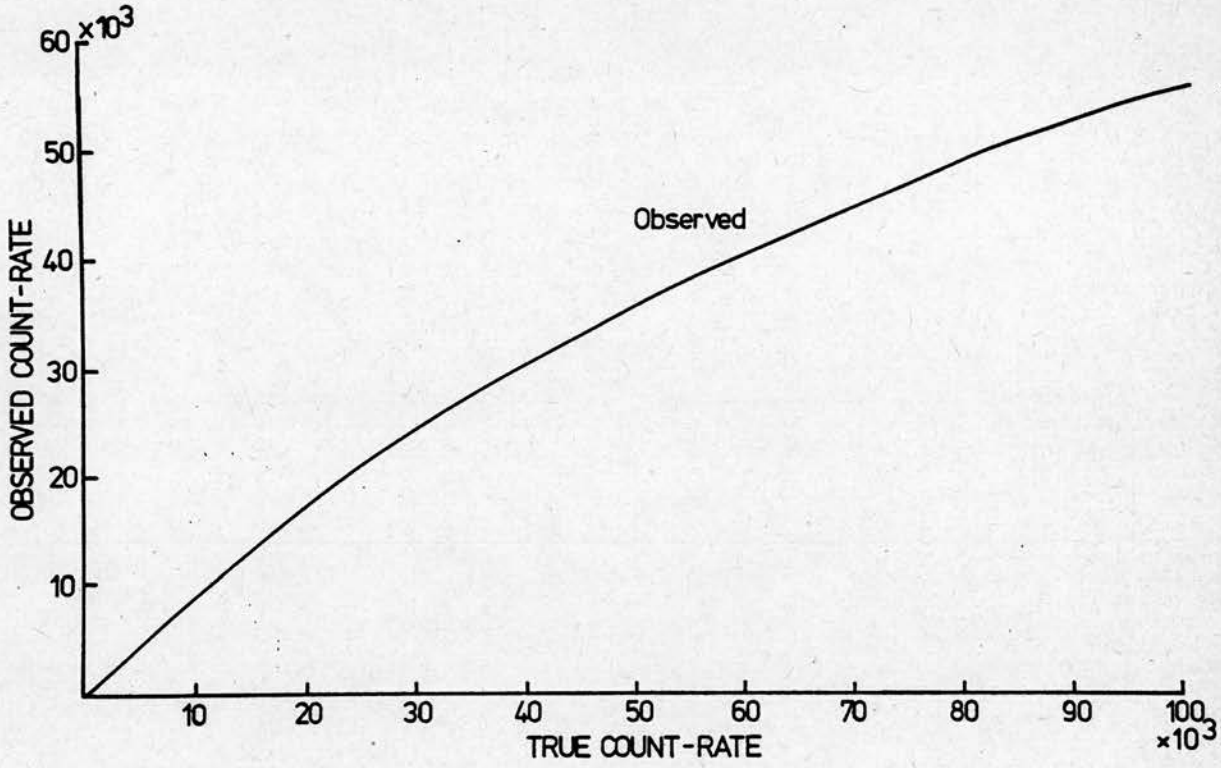


Figure 33

Illustrates the observed count rate at different true count rates. (After Hannan and Hare, 1976).

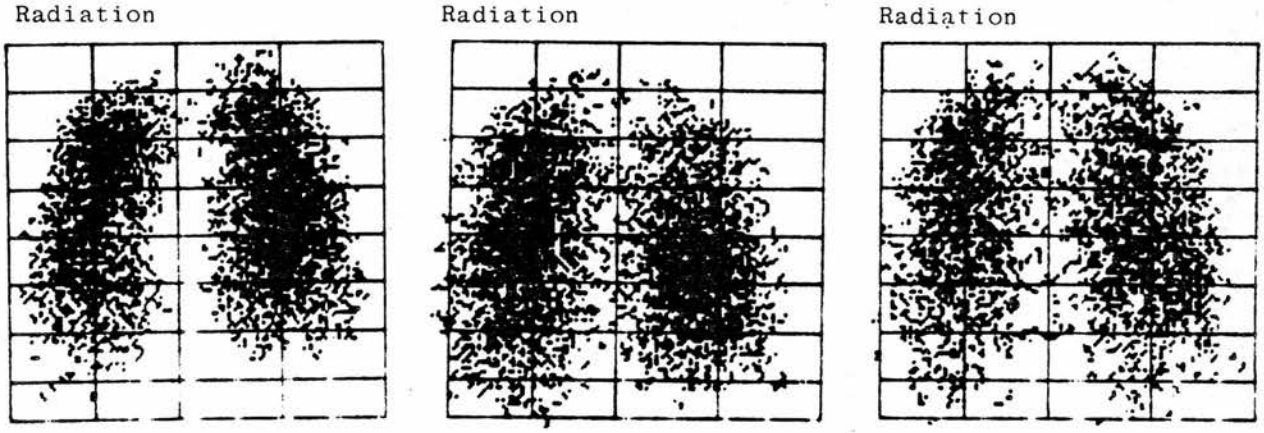
Analysis of the regional $\dot{V}/E$ and $\dot{Q}/E$ measurements

The count rates after any particular manoeuvre are always related to the count rates at TLC after rebreathing to equilibrium (E). The count rates at equilibration represent the distribution of the Xe^{133} in alveolar spaces, which are all equally distended at TLC (West, 1977), so correcting for difference regional lung volumes.

The actual count rates were either accumulated on a videotape for subsequent replay into a PDP 12 digital computer through the interface onto a 64 x 64 matrix, or the counts were taken directly from the gamma camera to an on-line PDP 11/34 computer. The data is then analysed on a regional basis, the sizes of the region being operator-chosen and usually are an 8 x 4 matrix; thus dividing the lung fields into 32 segments with 8 horizontal slices. The anatomical marker was used to set the midline which separated the two lungs, and a hard copy of the display on the VDU obtained from Tectronics 4010 Hard Copy Unit, as shown in Figure 34. The data was analysed on the assumption that counts at equilibration (E) at TLC represent the regional lung volumes, so that the percentage distribution of ventilation to region i (i = 1/32), i.e. (the ventilation/unit alveolus) was:

$$\frac{\dot{V}i}{\sum_{i=1}^{32}\dot{V}i} \times \frac{\sum_{i=1}^{32} Ei}{Ei} \times 100 = \dot{V}/E\% \quad \text{(Bake et al, 1974)}$$

REGIONAL LUNG FUNCTION OF A BREAST CANCER PATIENT AFTER RADIOTHERAPY



a. Perfusion b. Ventilation c. Equilibration

Figure 34

The two lungs, divided into 32 segments with 8 horizontal slices.

a. shows the regional perfusion distribution
b. shows the regional ventilation distribution
c. shows the regional lung volumes (equilibration)

Where the total matrix amounted to 32 cells (4 x 8), so that $i = \frac{1}{32}$

$\dot{V}i$ = the ventilation count rate in region i

$\sum_{i=1}^{32} \dot{V}i$ = the total ventilation count rate (i.e. $\dot{V}_{Tot}$) in all 32 cells of the matrix

Ei = the equilibration count rate to region i

$\sum_{i=1}^{32} Ei$ = the total equilibration count rate (i.e. E_{Tot}) in all 32 cells of the matrix

$\dot{V}/E\%$ = ventilation/unit alveolus % (i.e. % of that if it was not uniformly distributed by basis of lung volume)

Furthermore, using the same equation, the percentage distribution of perfusion to region i was:

$$\frac{\dot{Q}i}{\sum_{i=1}^{32} \dot{Q}i} \times \frac{\sum_{i=1}^{32} Ei}{Ei} \times 100 = \dot{Q}/E\%$$

Where $\dot{Q}i$ = the perfusion count rate in region i

$\sum_{i=1}^{32} \dot{Q}i$ = the total perfusion count rate (i.e. $\dot{Q}_{Tot}$) in all 32 cells of the matrix

$\dot{Q}/E\%$ = perfusion/unit alveolus % (i.e. % of that if it was uniformly distrubted by basis of lung volume)

On the other hand, the percentage of the total lung volume contained in that region ($\dot{V}i$) was calculated by the following formula:

$$\frac{\frac{Ei}{32}}{\sum_{i=1} Ei} \times 100 = Vi\%$$

assuming that at equilibration, when measured at TLC, all alveoli are uniformly distended

Where Vi% is the lung volume in region i, as a percentage of the total lung volume. Thereafter, the <u>average</u> of the two segments (inner and outer) in each vertical slice of the treated lung was compared to that of the same two segments in the same vertical slice of the untreated lung. This average value was calculated using the following formula:

$$\frac{\bar{\dot{V}}}{\bar{E}} = \frac{(\dot{V}1/E1).\ V1 + (\dot{V}2/E2).\ V2}{V1 + V2}$$

Where $\dot{V}1$ = $\dot{V}/E\%$ ($\dot{Q}/E\%$) of segment 1, slice I

$V1$ = Lung volume% of segment 1, slice I

$\dot{V}2$ = $\dot{V}/E\%$ ($\dot{Q}/E\%$) of segment 2, slice I

$V2$ = Lung volume% of segment 2, slice I

$\frac{\bar{\dot{V}}}{\bar{E}}$ = the weighted average (weighted to the lung volume) of the two segments in slice I for one lung

On the same principle, the weighted average of each of $\dot{V}/E\%$, $\dot{Q}/E\%$ and V% of the upper 3 slices in the treated lung were compared with those in the untreated lung. It was assumed that the upper 3 slices were the region of the treated lung which received the total ratiation dose of up to 4250 rads "to max", from the supra-clavicular and axillary fields I and II.

III RESULTS

i) Sequential Study

The "control" measurements prior to radiotherapy, but after simple mastectomy, are summarised in Table 1 for all 10 patients. The age range of these patients was 35-61 years, with an average of 49.4 years. One patient (2) was a smoker, one patient (7) was an ex-smoker and the rest were non-smokers. The average height was 1.67 metres and the average weight was 66.6 kilograms. The pathological type of tumour and the stage was also recorded, as was the side of the tumour; on the right in 4 patients and on the left in the rest (Table 1). Haemoglobin concentration (Hb) and white blood cell (WBC) count in the venous blood were normal in all but one (9), who was mildly anaemic. The electrocardiogram was normal for all but one (4), who had first degree heart block (1^{o}H.B.). The chest x-ray was also normal in all patients. The overall lung function measurement values are given as mean $\pm$ SEM.

1. Results of the overall lung function measurements

These measurements showed that the mean total lung capacity (TLC) was 5.70 $\pm$ 0.2 litres (111.9 $\pm$ 3.3% of predicted normal values), vital capacity (VC) was 3.48 $\pm$ 0.2 litres (113.6 $\pm$ 6.1% predicted), residual volume (RV) was 2.22 $\pm$ 0.2 litres (125.9 $\pm$ 12.5% predicted) (Tables 1,12). The finding that the residual volume was consistently higher than that predicted resulted from these measurements being

made by the body plethysmograph, whereas the predicted values were made by the Helium dilution method. Thus in a separate study of 26 subjects (12 normal and 14 patients with chronic obstructive lung disease) studied twice by both the Helium dilution method and by the body plethysmograph, the plethysmographic values for RV were higher than those using the He-dilution method (Figure 35).

The mean RV/TLC% ratio was 39 $\pm$ 4 (111.3 $\pm$ 10.0% predicted). The mean $FEV_{1.0}$ was 2.72 $\pm$ 0.2 litres (119.0 $\pm$ 7.3% predicted), FVC was 3.21 $\pm$ 0.3 litres (110.8 $\pm$ 8.5% predicted) and $FEV_1/FVC\%$ was 85 $\pm$ 2.1 (107.4 $\pm$ 2.3% predicted) (Tables 1,12), which were all within the normal limits.

$\dot{V}_{max}$ 50 (maximum flow at 50% VC) and $\dot{V}_{max}$ 30 (maximum flow at 30% VC) were not measured in 2 patients (1,2), but were normal for the rest, with a mean $\dot{V}_{max}$ 50 of 3.57 $\pm$ 0.4 litres/sec and a mean $\dot{V}_{max}$ 30 of 1.83 $\pm$ 0.25 litres/sec (Tables 1,12). The mean transfer factor for carbon monoxide (T_{CO}) was 6.60 $\pm$ 0.4 mmol/min/kPa (76.7 $\pm$ 4.8% predicted), some of these patients (2,4,7) being below the predicted normal values in the "control" study, even before radiotherapy (Tables 1,12). The mean specific conductance (sGaw) was 1.240 $\pm$ 0.10 $sec.^{-1}kPa^{-1}$ in 8 patients.

Following radiotherapy these studies of overall lung function were repeated at 1 month, 3 months, 6 months, 9 months and 12 months for each patient (Tables 2-11). A summary of the results of these measurements, with the mean and standard error, is shown in Table 12 and also in Figure 36 and Figure 37.

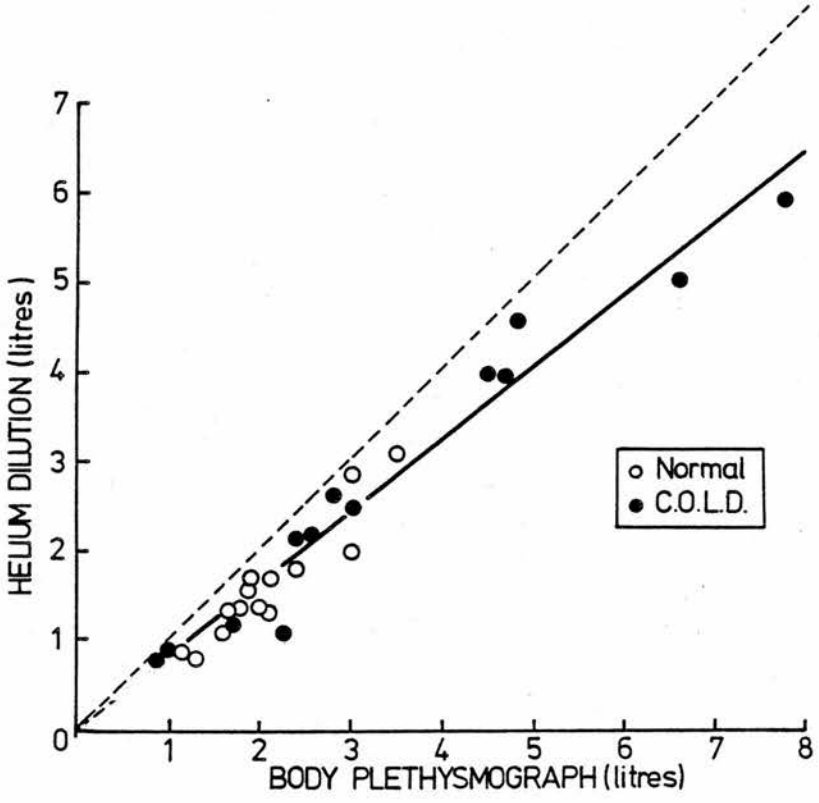


Figure 35

The residual volume (RV) values in litres as measured with the Helium dilution (y-axis) and the body plethysmograph (x-axis) in normal subjects (o) and in patients with chronic obstructive lung disease (•).

----- the line of indentity

——— the regression line

$y = xb+a$

$r = 0.9797$

The mean VC at 1 month was 3.56 ± 0.2 litres (116.9 ± 5.2% predicted), at 3 months was 3.47 ± 0.2 litres (111.0 ± 5.3% predicted), at 6 months was 3.34 ± 0.2 litres (105.5 ± 5.4% predicted), at 9 months was 3.34 ± 0.2 litres (105.5 ± 6.3% predicted) and at 12 months was 3.33 ± 0.2 litres (106.6 ± 6.2% predicted), all of which showed no significant change from the control values (Table 12). The RV/TLC% also showed no significant changes from their control values before radiotherapy. FVC did not change following radiotherapy, as compared to the control values (Table 12, Figure 36) and the mean $\dot{V}_{max}$ 50 was 3.55 ± 0.5 L/sec at 1 month, 3.53 ± 0.48 L/sec at 3 months, 3.51 ± 0.45 L/sec at 6 months, 3.52 ± 0.52 L/sec at 9 months and 3.59 ± 0.54 L/sec at 12 months, again showing no significant difference as compared to their control value. The mean values of $\dot{V}_{max}$ 30 at different intervals following radiotherapy showed no significant differences, as compared to their control value (Table 12).

The mean T_{CO} at 1 month was 6.52 ± 0.3 mmol/min/kPa (75.9 ± 3.1% predicted), at 3 months was 6.72 ± 0.2 mmol/min/kPa (77.6 ± 2.4% predicted), at 6 months was 6.95 ± 0.2 mmol/min/kPa (80.7 ± 2.9% predicted), at 9 months was 6.61 ± 0.2 mmol/min/kPa (77.2 ± 4.3% predicted) and at 12 months was 6.76 ± 0.25 mmol/min/kPa (78.9 ± 4.4% predicted), which showed no significant change as compared to their control values (Table 12, Figure 36). The mean sGaw at 1 month was 1.41 ± 0.14 $sec.^{-1}kPa^{-1}$, at 3 months was 1.27 ± 0.12 $sec.^{-1}kPa^{-1}$, at 6 months was 1.42 ± 0.15 $sec.^{-1}kPa^{-1}$, at 9 months was

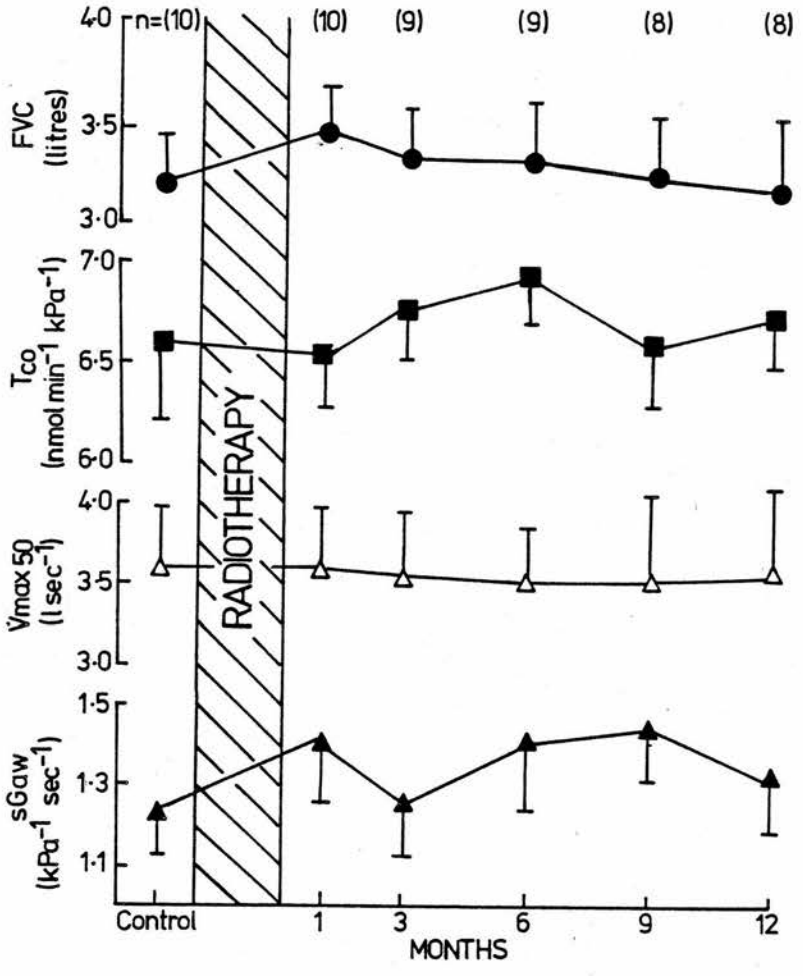


Figure 36

The means and standard error of the forced vital capacity (litres), transfer factor for carbon monoxide (mmol/min/kPa), maximum flow rate at 50% vital capacity (L/sec) and specific airways conductance ($kPa^{-1}.sec^{-1}$) of 10 patients studied before radiotherapy, but after mastectomy, and at 1,3,6,9 and 12 months after radiotherapy. There was no significant difference after radiotherapy, as compared to control values for all these variables.

1.48 ± 0.15 sec.$^{-1}$kPa^{-1} and at 12 months was 1.33 ± 0.14 sec.$^{-1}$kPa^{-1}. These values were also not significantly different from the control values (Table 12, Figure 36).

However, the mean TLC was 5.48 ± 0.2 litres (107.7 ± 3.9% predicted) at 1 month, 5.40 ± 0.2 litres (104.0 ± 3.5% predicted) at 3 months, 5.17 ± 0.1 litres (99.6 ± 1.7% predicted) at 6 months, 5.05 ± 0.1 litres (97.6 ± 2.5% predicted) at 9 months and 5.19 ± 0.1 litres (100.1 ± 1.2% predicted) at 12 months (Table 12, Figure 37). The results suggest that the radiotherapy caused a reduction in mean TLC value which was significant ($P < 0.05$) at 1 month and more significant ($P < 0.01$) at 6, 9 and 12 months after radiotherapy, using paired t-test.

The mean RV was 1.97 ± 0.15 litres (110.4 ± 10.2% predicted) at 1 month, 1.94 ± 0.25 litres (109.6 ± 12.0% predicted) at 3 months, 1.83 ± 0.2 litres (104.9 ± 9.2% predicted) at 6 months, 1.75 ± 0.2 litres (94.2 ± 10.4% predicted) at 9 months and 1.86 ± 0.2 litres (98.5 ± 10.0% predicted) at 12 months (Table 12, Figure 37). These values at 1 and 3 months were not significantly lower than the control values, but at 6, 9 and 12 months the mean RV were significantly lower ($P < 0.05$) than the control values, implying that radiotherapy also reduced the mean RV.

The mean FEV_1 was 2.73 ± 0.2 litres (119.7 ± 7.6% predicted) at 1 month, 2.67 ± 0.2 litres (115.0 ± 8.5% predicted) at 3 months, 2.71 ± 0.25 litres (116.4 ± 9.4% predicted) at 6 months, 2.65 ± 0.3 litres (113.8 ± 10.5% predicted) at 9 months and 2.61 ± 0.3 litres (112.2 ± 10.5% predicted) at 12 months (Table 12, Figure 37). Although the

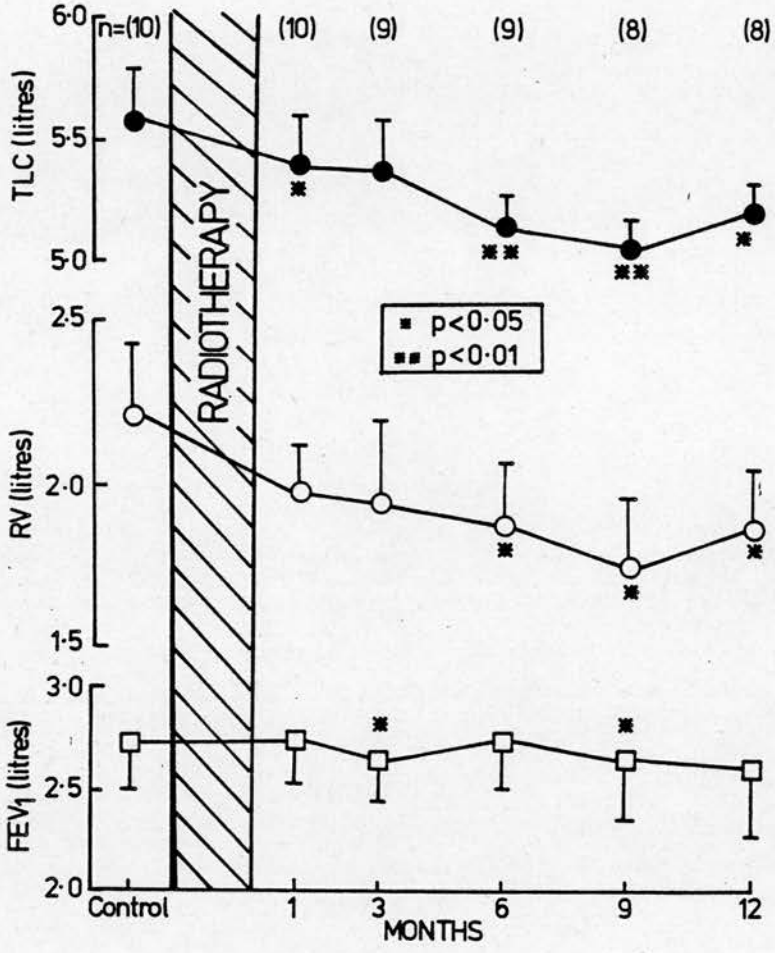


Figure 37

The means and standard errors of total lung capacity (litres), residual volume (litres) and forced expiratory volume at 1.0 sec (litres) of 10 patients studied before radiotherapy, but after mastectomy, and at 1,3,6,9 and 12 months after radiotherapy. There was significant reduction at the 5% and 1% levels after mastectomy, as compared to the control values in these patients.

mean FEV_1 values at 1 and 6 months were not significantly different from the control values, those at 3, 9 and 12 months were significantly lower ($P < 0.05$) than the control values. Although this reduction in mean FEV_1 after radiotherapy was statistically significant, it was only 0.12 litres. The mean values of the ratio of $FEV_1/FVC\%$ at 1, 3 and 6 months were also significantly lower ($P < 0.05$) than the control value (Table 12); yet the mean $FEV_1/FVC\%$ at 9 and 12 months was not significantly lower than the control value. The overall lung function results for individual patients will be mentioned later.

2. Results of regional lung function measurements

The regional distribution of perfusion/unit alveolus% ($\dot{Q}/E\%$), ventilation distribution/unit alveolus% ($\dot{V}/E\%$) at two flow rates (0.2 L/sec and 1.5 L/sec), lung volume% (V%) were measured in 8 horizontal segments of each lung in each individual patient. These results are shown in separate tables, for each variable, in each individual patient and will be mentioned later.

The results were also calculated as the average values for the upper 3 segments of the irradiated lung and the same values of the non-irradiated (control) lung, and also the differences between these average values in the two lungs for each variable, i.e. for $\dot{Q}/E\%$ (Tables 1,13), for V% (Tables 1,14), for $\dot{V}/E\%$ at 0.2 L/sec (Tables 1,15) and for $\dot{V}/E\%$ at 1.5 L/sec (Tables 1,16). These measurements were made in 10 patients in the control study before radiotherapy but after simple mastectomy and at 1 month,

3 months, 6 months, 9 months and 12 months after radiotherapy. However, the mean values calculated for each variable included only 7 patients (1,3,4,6,8,9,10) because it is believed (as will be mentioned later) that in two patients (5,7) there were serious technical errors in these values from malpositioning; therefore these two patients were excluded from the study in calculation of the mean values. Furthermore, patient (2) was not included as she declined further study after one month.

The results are expressed as differences between the averages (irradiated - non-irradiated), not ratios (irradiated/non-irradiated) since these ratios were not normally distributed. Thus, differences of the average values for each of these variables were plotted against time after radiotherapy, the trend of changes being observed at each period after radiotherapy and also the values at 1, 3, 6, 9 and 12 months being each compared to those values at the control study using the paired 't' test as well as Wilcoxon's statistical tests of significance for paired difference.

The mean perfusion per alveolus ($\dot{Q}/E\%$) of the difference between irradiated and non-irradiated averages of the upper 3 segments at the control study was $-0.6 \pm 2.9\%$, so that the irradiated lung apex was not significantly less perfused than the non-irradiated lung apex, as shown in Tables 1,13 and Figure 38. Following radiotherapy, each patient behaved differently, but the trend of the mean values of $\dot{Q}/E\%$ showed a reduction in perfusion of the irradiated lung apex, the

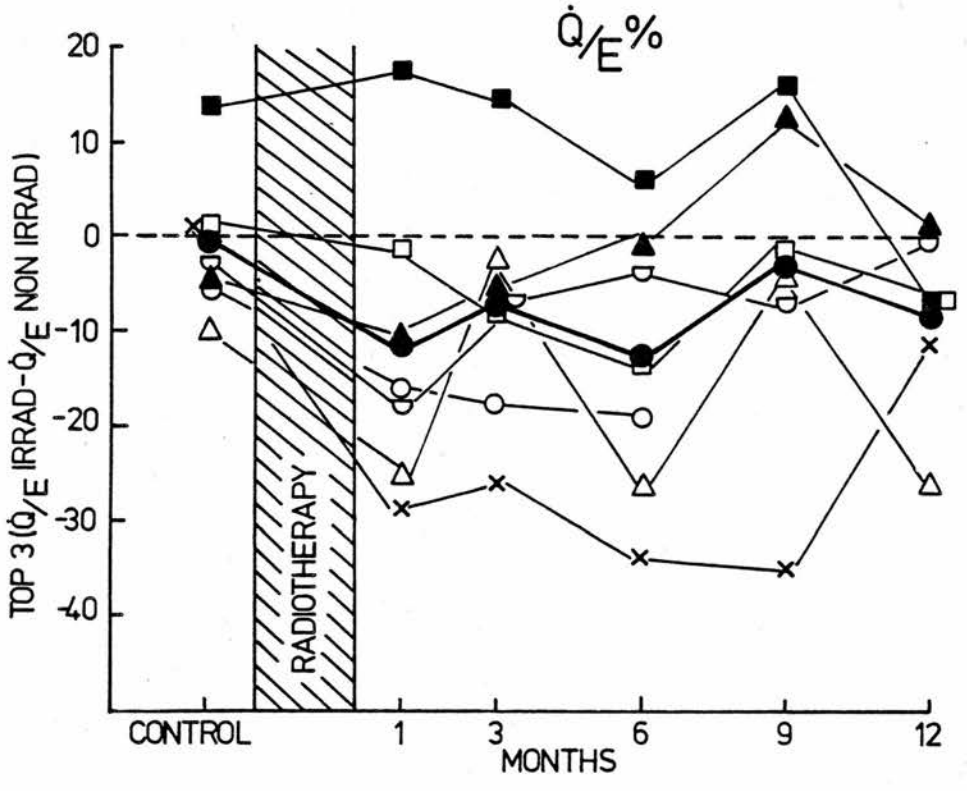


Figure 38

The perfusion/alveolus % calculated as the difference between the average value of the upper 3 segments of the irradiated lung and those of the non-irradiated lung for 7 patients, plotted against time in months - studied before radiotherapy, but after mastectomy, and at 1,3,6,9 and 12 months after radiotherapy. The dotted line shows zero difference between the two lungs. The dark line is the mean values for these patients. There was no significant difference between the upper zones of the 2 lungs before radiotherapy. However, there was significant reduction ($P < 0.05$) of perfusion/alveolus in the irradiated upper zone at 1 month and at 6 months after radiotherapy as compared to the control, but was not significant at 3,9 and 12 months after radiotherapy, as compared to the control.
(x) patient 1; (⊃) patient 3; (△) patient 4; (▲) patient 6;
(o) patient 8; (■) patient 9; (□) patient 10; (●) the Mean.

mean difference being -11.3 ± 5.9% (Table 13, Figure 38) at one month study. This reduction (mean difference) was statistically significant ($P < 0.05$) from the mean level of difference between the two sides in the control study. However, at 3 months the mean difference of $\dot{Q}/E\%$ was -7.1 ± 4.8%. This was lower than the control value, but not significantly different from it (Table 13, Figure 38); whereas at 6 months the mean $\dot{Q}/E\%$ difference was -12.9 ± 5.5%, which was significantly lower ($P < 0.05$) than that in the control study. However, at 9 months the mean $\dot{Q}/E\%$ (-3.0 ± 7.4%) was again not statistically different from the mean difference in the control study (Table 13, Figure 38). Moreover, at 12 months the mean $\dot{Q}/E\%$ difference was -8.3 ± 4.1%, again not statistically different from that in the control study.

The mean difference of regional lung volume (V%) (Tables 1,14 and Figure 39) was -0.19 ± 0.2% at the control study, -0.3 ± 0.5% at 1 month, -0.29 ± 0.4% at 3 months, 0.07 ± 0.2% at 6 months, -0.28 ± 0.2% at 9 months and -0.37 ± 0.2% at 12 months. All these values were not significantly different from that in the control study. The mean difference of ventilation per alveolus ($\dot{V}/E\%$) at 0.2 L/sec showed also non-significant change following radiotherapy, as compared to the control values (Tables 1,15 and Figure 40). The mean difference of the averages (irradiated upper 3 segments - non-irradiated upper 3 segments) at the control study was 0.06 ± 4.5%, at 1 month was -5.4 ± 6.2%, at 3 months was -6.5 ± 5.9%, at 6 months was 7.2 ± 5.7%, at 9 months was -0.8 ± 3.8% and at 12

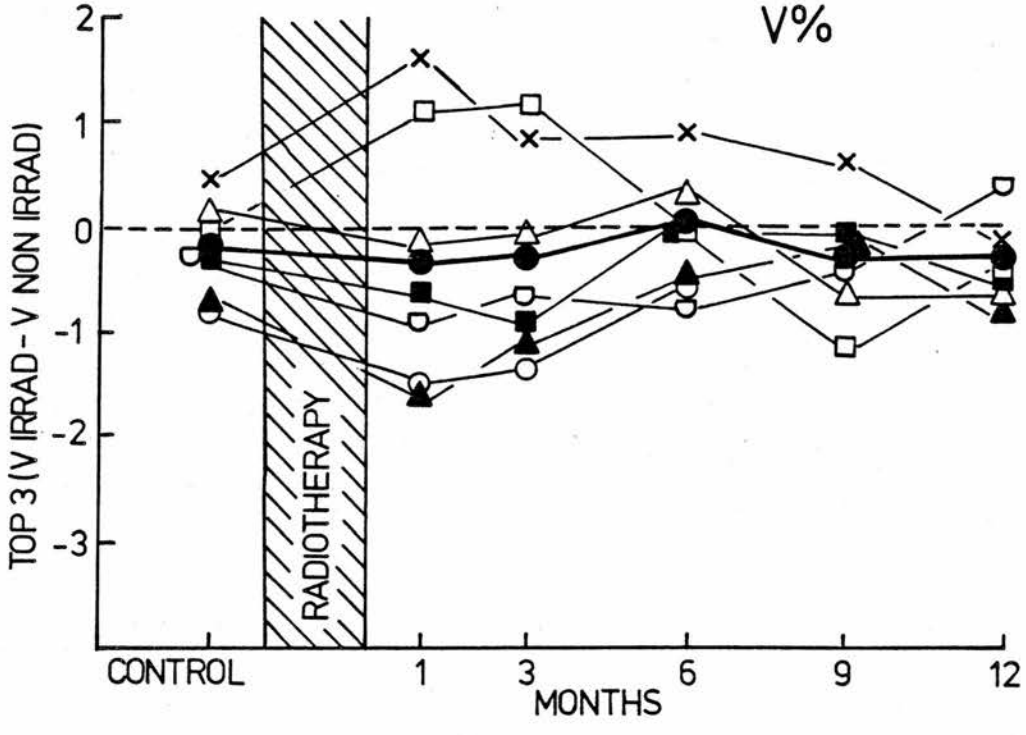


Figure 39

The lung volume % calculated as the difference between the average value of the upper 3 segments of the irradiated lung and those of the non-irradiated lung for 7 patients, plotted against time in months - studied before radiotherapy, but after mastectomy, and at 1,3,6,9 and 12 months after radiotherapy. The dotted line shows zero difference between the two lungs. The dark line is the mean values for these patients. There was no significant difference between the upper zones of the two lungs either before radiotherapy or after radiotherapy.

(x) patient 1; (ⵔ) patient 3; (△) patient 4; (▲) patient 6; (o) patient 8; (■) patient 9; (□) patient 10; (●) the Mean.

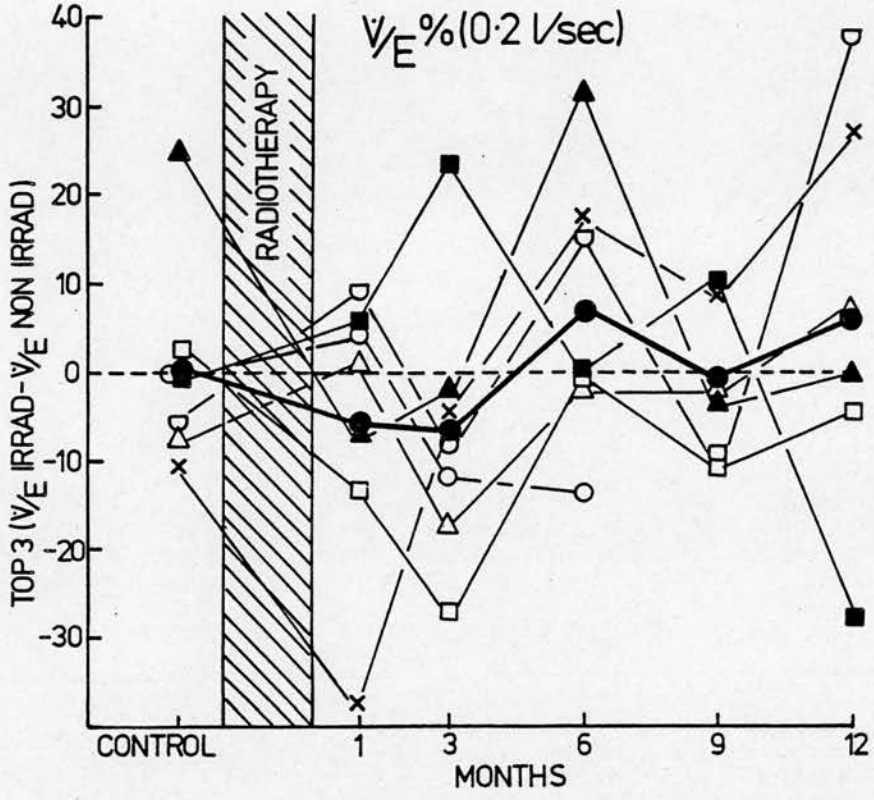


Figure 40

The ventilation/alveolus % at inspiratory flow rate of 0.2 L/sec, calculated as the difference between the average value of the upper 3 segments of the irradiated lung and those of the non-irradiated lung for 7 patients, plotted against time in months - studied before radiotherapy, but after mastectomy, and at 1,3,6,9 and 12 months after radiotherapy. The dotted line shows zero difference between the two lungs. The dark line is the mean values for these patients. There was no significant difference between the upper zones of the 2 lungs either before radiotherapy or after radiotherapy.
(x) patient 1; (◫) patient 3; (△) patient 4; (▲) patient 6; (o) patient 8; (■) patient 9; (□) patient 10; (●) the Mean.

it was 6.7 ± 9.6%.

The mean difference of the averages of ventilation per alveolus ($\dot{V}/E\%$) at 1.5 L/sec at the 6 months study was significantly greater ($P < 0.05$) than the mean difference of the averages of the control study (Figure 41); where the mean difference at the control study was -7.0 ± 3.8%, at 1 month was 1.9 ± 2.5%, at 3 months was 5.4 ± 3.6%, these not being significantly different from the control value. At 6 months the mean difference was 10.4 ± 3.5%, which is significantly greater than the control value ($P < 0.05$). This ventilation change gradually returned to normal at 9 and 12 months, where the mean difference at 9 months was -0.78 ± 3.3% and at 12 months was 6.07 ± 3.0% (Tables 1,16 and Figure 41).

3. Overall and regional lung function results for individual patients

Patient 1

This 46 year old woman had a poorly differentiated stage II carcinoma of the right breast treated with simple mastectomy and radiotherapy. The minimum radiation dose to the right lung apex was 4035 rads. She was a non-smoker; her height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements, the ECG and chest x-ray findings during the control study. Following radiotherapy (Tables 12,2A), this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC fell by 1.34 litres at 6 months and 1.21 litres at 12 months,

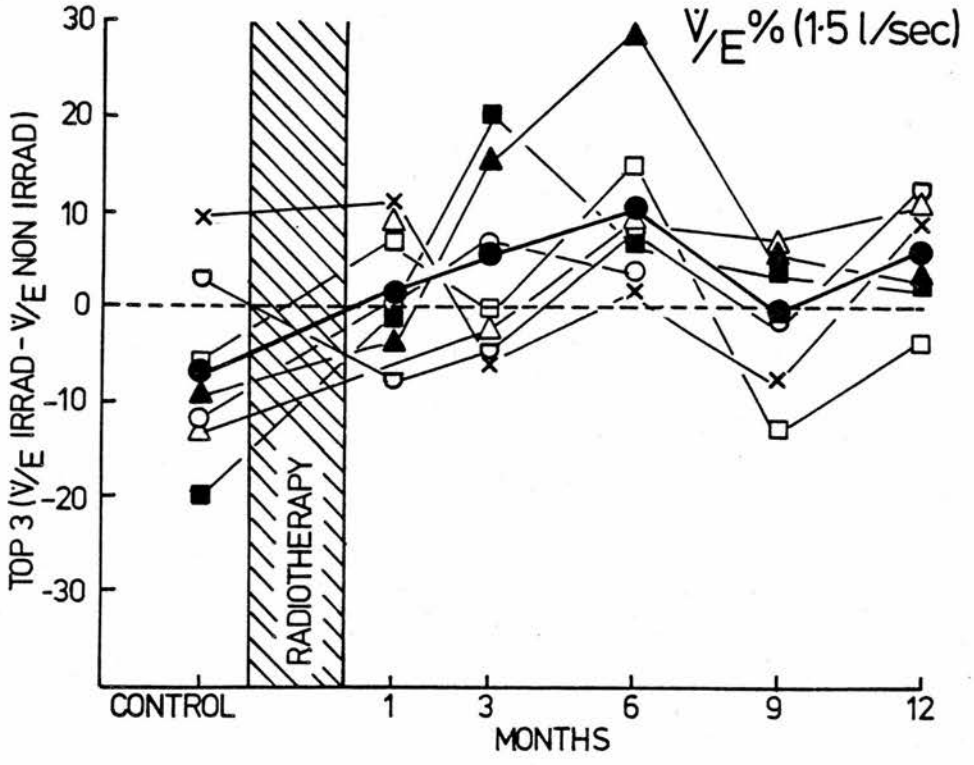


Figure 41

The ventilation/alveolus % at inspiratory flow rate of 1.5 L/sec, calculated as the difference between the average value of the upper 3 segments of the irradiated lung and those of the non-irradiated lung for 7 patients, plotted against time in months - studied before radiotherapy, but after mastectomy, and at 1,3,6,9 and 12 months after radiotherapy. The dotted line shows zero difference between the two lungs. The dark line is the mean values for these patients. There was no significant difference between the upper zones of the 2 lungs before radiotherapy and at 1,3,9 and 12 months after radiotherapy. There was significant increase ($P < 0.05$) of ventilation/alveolus in the irradiated upper zone at 6 months after radiotherapy, as compared to the control value.
(x) patient 1; (◑) patient 3; (△) patient 4; (▲) patient 6; (o) patient 8; (■) patient 9; (□) patient 10; (●) the Mean.

but these values were still within the normal range (i.e. predicted value $\pm$ 2 x S.D.) for a women of her age and height. Her RV fell by 0.95 litres at 6 months and 0.87 litres at 12 months, but was also still within her normal ranges. Her FEV_1 and the other overall lung function measurements were within the normal range. No change was found in her ECG or the chest x-ray following radiotherapy (Table 2A, Figure 42). The regional lung function, as calculated for each variable, ($\dot{Q}$/E%, V%, $\dot{V}$/E% at 0.2 L/sec and $\dot{V}$/E% at 1.5 L/sec) in 8 horizontal segments of each lung and the differences between the irradiated segments and the non-irradiated segments were calculated (Tables 2B,2C,2D,2E) and plotted against the corresponding segments (Figures 43,44,45,46) and sequentially with time after radiotherapy.

The regional lung function was also calculated as the difference between the average of the upper 3 segments of the irradiated lung and that of the upper 3 segments of the non-irradiated lung (Tables 1,13,14,15,16). These differences were also plotted against time following radiotherapy (Figures 36,37,38,39). The difference between the average $\dot{Q}$/E% for the upper 3 segments of the irradiated lung and those of the non-irradiated lung was 0.6% in the control measurements. At one month this difference became -28.5% (i.e. the $\dot{Q}$/E% of the irradiated lung in the upper 3 segments decreased), at 3 months this difference was -25.7%, at 6 months it became -33.9%, at 9 months it was -34.7% and at 12 months this difference became less and was -11.1%. These values showed that the $\dot{Q}$/E% of the

(A) (B)

Figure 42

The chest x-ray of patient 1 at the "control" study (A) and at 6 months after radiotherapy (B). The marked area received a minimum radiation dose of 4035 rads.

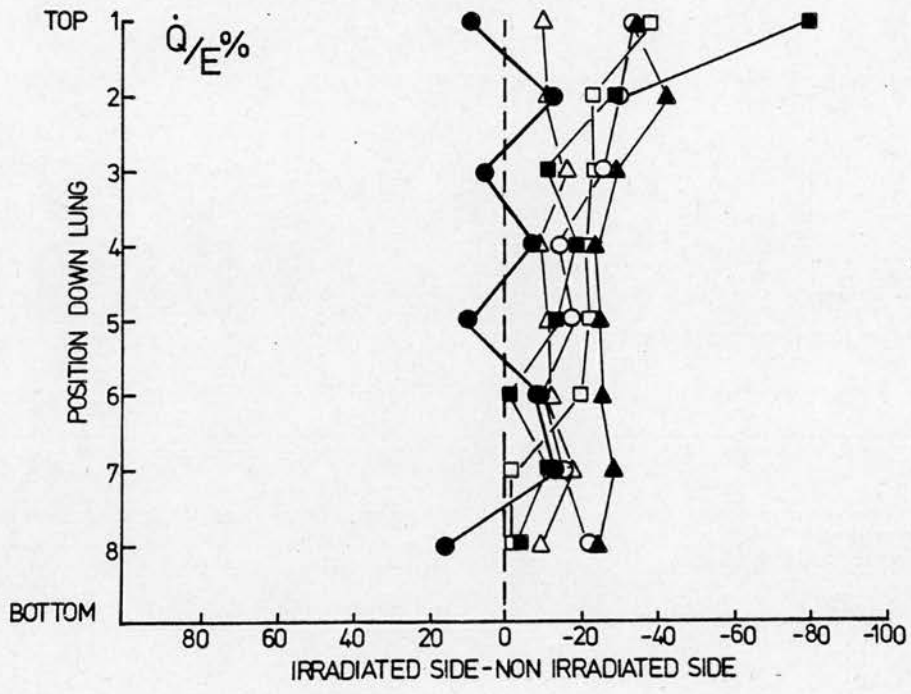


Figure 43

The difference in the regional distribution of perfusion in 8 horizontal segments of the irradiated lung and those of the non-irradiated lung in patient 1.
(●) pre-radiotherapy "control"; (o) 1 month study;
(□) 3 months study; (■) 6 months study; (▲) 9 months study;
(△) 12 months study.

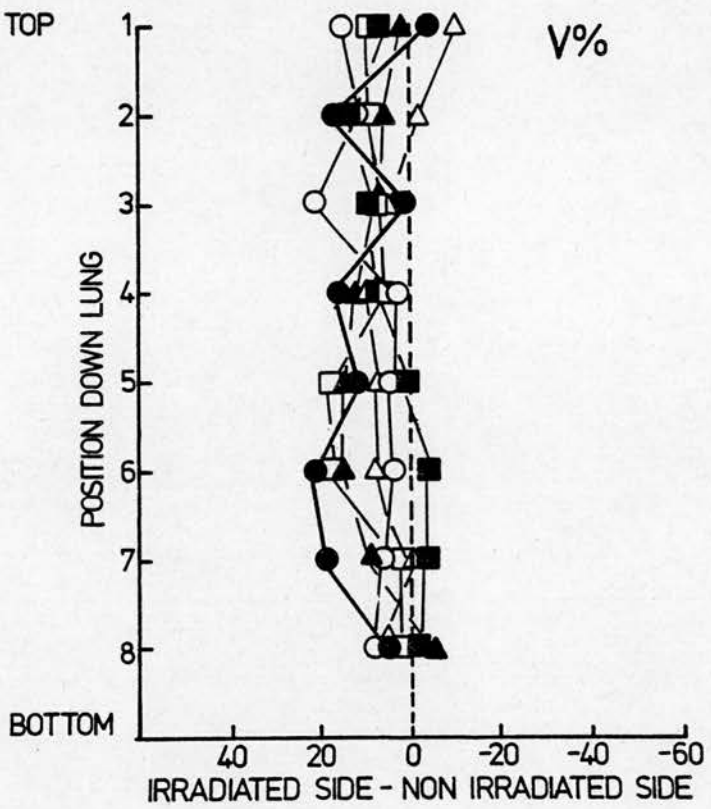


Figure 44

The difference in the regional lung volume distribution in 8 horizontal segments of the irradiated lung and those of the non-irradiated lung in patient 1.
(●) pre-radiotherapy "control"; (o) 1 month study;
(□) 3 months study; (■) 6 months study; (▲) 9 months study;
(△) 12 months study.

upper segment of the irradiated lung fell, as compared to those of the non-irradiated lung and this reduction was worse at 6 months and 9 months, but it tended to improve at 12 months in this patient (Table 13, Figure 38).

The difference between the average values of the regional lung volume (V%) in the upper 3 segments of the irradiated and those of the non-irradiated lung was 0.47% in the control measurments, 1.6% at 1 month, 0.84% at 3 months, 0.9% at 6 months, 0.63% at 9 months and -0.14% at 12 months (Table 14, Figure 39). These values were within the normal ranges for such measurements.

The difference between the average of the upper 3 segments of the irradiated lung and that of the non-irradiated lung for $\dot{V}/E\%$ at 0.2 L/sec was -10.8% at the control measurements, -37.9% at 1 month, -4.8% at 3 months, 17.3% at 6 months, 9.7% at 9 months and 26.9% at 12 months (Table 15, Figure 40). These values showed reduction in ventilation at 1 month, which was increased thereafter. The difference for $\dot{V}/E\%$ at 1.5 L/sec was 9.7% at the control measurements, 10.1% at 1 month, -6.0% at 3 months, 1.3% at 6 months, -7.9% at 9 months and 9.3% at 12 months (Table 16, Figure 41). These changes showed reduction in $\dot{V}/E\%$ at 3 months which almost returned to normal at 12 months.

Patient 2

This 61 year old woman had a highly sclerosing stage I carcinoma of the right breast treated with simple

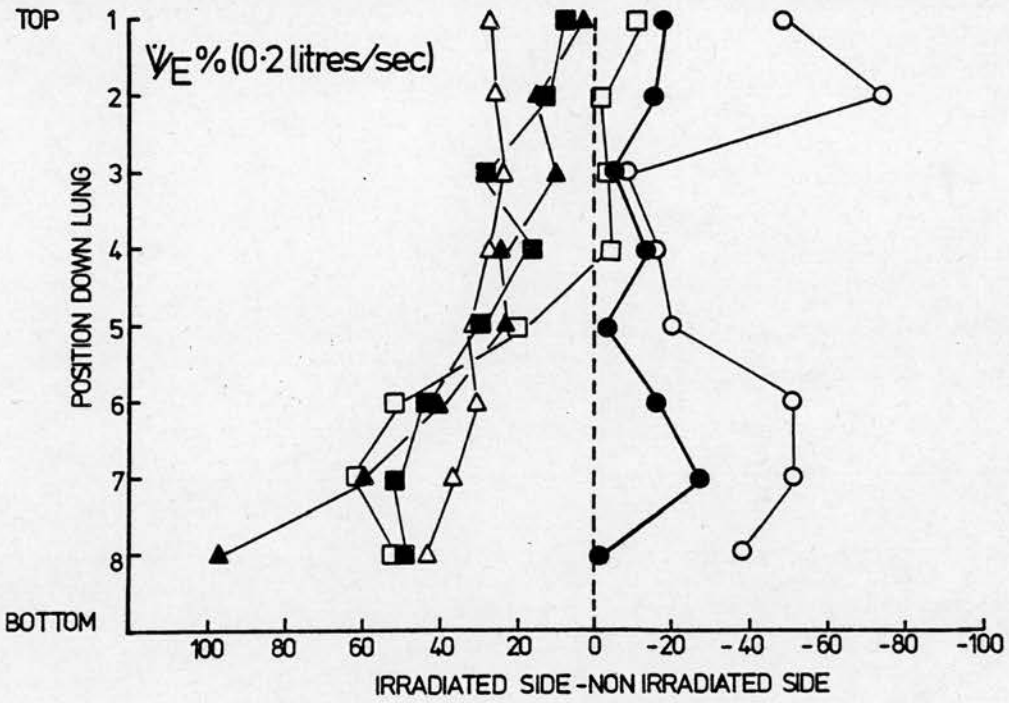


Figure 45

The difference in the regional distribution of ventilation (0.2 L/sec) in 8 horizontal segments of the irradiated lung and those of the non-irradiated lung in patient 1. (●) pre-radiotherapy "control"; (o) 1 month study; (□) 3 months study; (■) 6 months study; (▲) 9 months study; (△) 12 months study.

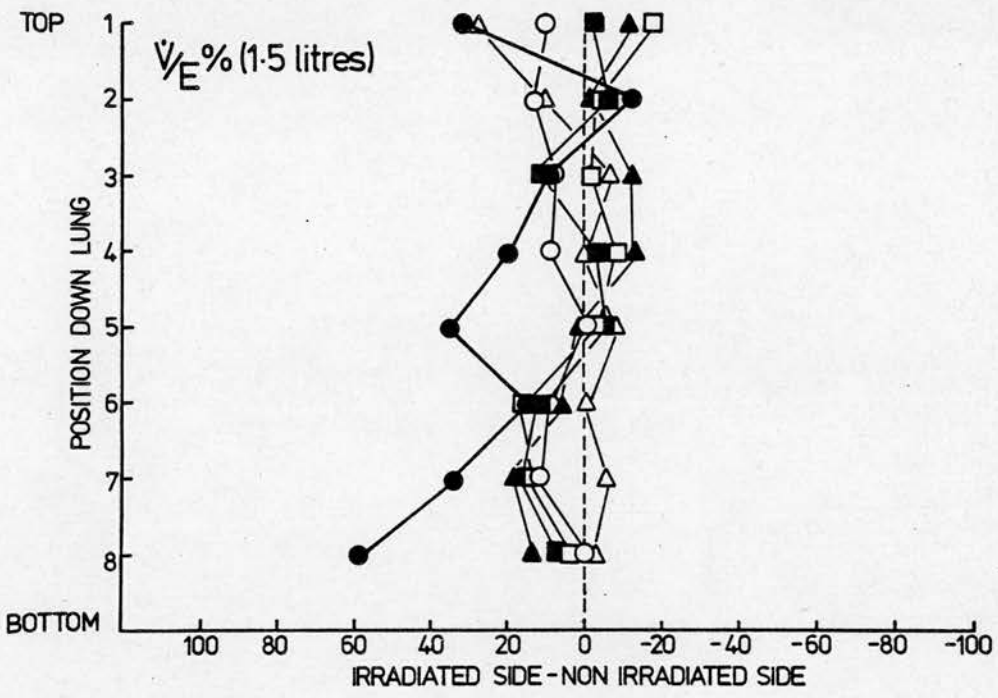


Figure 46

The difference in the regional distribution of ventilation (1.5 L/sec) in 8 horizontal segments of the irradiated lung and those of the non-irradiated lung in patient 1. (●) pre-radiotherapy "control"; (o) 1 month study; (□) 3 months study; (■) 6 months study; (▲) 9 months study; (Δ) 12 months study.

mastectomy and radiotherapy. The minimum radiation dose to the right lung apex was 4070 rads. She was a smoker; her height, weight, haemoglobin, WBC count, overall and regional lung function measurements are shown in Table 1, together with the ECG and chest x-ray findings at the control period. Following radiotherapy (Tables 12,3A) this patient was studied at 1 month and she declined further study. Thereafter another study was carried out on her at 24 months. Her TLC was not changed at 1 month or at 24 months, nor were her RV values. Her ECG was normal at 1 month and at 24 months. Moreover, the chest x-ray showed no changes at 1 month and at 24 months (Table 3A). Her regional lung function, as calculated for each variable ($\dot{Q}$/E%, V%, $\dot{V}$/E% at 0.2 L/sec and $\dot{V}$/E% at 1.5 L/sec) in the 8 horizontal segments for each lung, together with the differences between the irradiated segments and the non-irradiated segments at the control study and at 1 month and 24 months after radiotherapy are shown in Tables 3B,3C, 3D and 3E.

The averages of the upper 3 segments of the irradiated lung and those of the non-irradiated lung for each variable was calculated, together with the differences between these averages for each variable (Tables 13,14,15,16). The results of this patient were not included in the calculation of the mean of the group in the sequential study as she declined further study after one month.

Patient 3

This 54 year old woman had an anaplastic stage II carcinoma of the left breast treated with simple mastectomy

and radiotherapy. The minimum radiation dose to the left lung apex was 4114 rads. She was a non-smoker; height, weight, haemoglobin and WBC count, overall and regional lung function measurements at the control period are shown in Table 1, together with her ECG and chest x-ray findings, which were normal. Following radiotherapy (Tables 12,4A) this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC fell by 0.61 litres at 6 months, by 0.84 litres at 9 months and by 0.55 litres at 12 months, although these values for TLC were within her predicted normal range (i.e. predicted $\pm$ 2 x S.D.). Her RV reduced by 0.77 litres at 6 months, by 1.19 litres at 9 months and by 0.81 litres at 12 months. These values for RV were also within the predicted normal range for this patient. FEV_1 reduced by 0.60 litres at 12 months after radiotherapy, as compared to her control value. Moreover, $\dot{V}_{max}$ 50 was reduced by 0.89 L/sec at 6 months and by 1.21 L/sec at 12 months; also $\dot{V}_{max}$ 30 was reduced by 0.42 L/sec at 6 months and by 1.21 L/sec at 12 months (Table 4A). T_{CO}, on the other hand, did not change and neither did sGaw. The chest x-ray was normal throughout the study (Tables 1,4A); whereas the ECG showed T wave changes starting at 3 months after radiotherapy with a T inverted (↓) in III and flat T in avf which persisted through all the study and, in addition, at 6 months showed flat T in all the leads, at 9 months showed biphasic T wave in V_{4-5} and at 12 months showed ST depression in leads II, avf and V_{5-6}.

The regional lung function was again calculated for each variable ($\dot{Q}$/E%, V%, $\dot{V}$/E% at 0.2 L/sec and $\dot{V}$/E% at 1.5 L/sec) in the 8 horizontal segments, together with the differences

between the irradiated and the non-irradiated lung segments (Tables 4B,4C,4D,4E).

The averages of the upper 3 segments for each lung and the difference between the irradiated and the non-irradiated average are shown in Tables 1,13,14,15,16, at the control study and at the different periods after radiotherapy. The difference of the averages was plotted sequentially against time for each variable and as shown in Figures 38,39,40,41. The irradiated side showed reduction in the $\dot{Q}/E\%$ at 1 month, down to a difference of -15.2%, as compared to a difference of -0.2% in the control measurement. However, at 3 months the difference was -6.2%, at 6 months was -3.8% and at 12 months the difference between the average of $\dot{Q}/E\%$ of the upper 3 irradiated segments and those of the non-irradiated segments was zero (Figure 38). The lung volume (V%) average of the upper 3 segments and the difference between the irradiated and the non-irradiated average are shown in Table 14, Figure 39 and were not changed significantly throughout the study in this patient. The averages of the upper 3 segments for $\dot{V}/E\%$ at 0.2 L/sec and at 1.5 L/sec are shown in Tables 15,16 respectively, together with the difference between the irradiated and the non-irradiated average at each study and the differences for these two variables were plotted against time following radiotherapy (Figures 40,41). These differences for $\dot{V}/E\%$ at 1.5 L/sec were unchanged through time; whereas those for $\dot{V}/E\%$ at 0.2 L/sec showed -5.9% at the control, 9.3% at 1 month, -5.6% at 3 months, 15.9% at 6 months,

-10.1% at 9 months and 38.1% at 12 months.

Patient 4

This 43 year old woman had an anaplastic stage I carcinoma of the left breast treated with simple mastectomy and radiotherapy. The minimum radiation dose to the left lung apex was 4115 rads. She was a non-smoker; her height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements, ECG and chest x-ray findings at the control study, which were normal. Following radiotherapy (Tables 12,5A) this patient was studied at 1, 3, 6, 9 and 12 months. The TLC was reduced by 0.42 litres at 6 months and by 0.54 litres at 12 months, but these values were within her predicted normal range (i.e. predicted $\pm$ 2 x S.D.). The RV and FEV_1, $\dot{V}_{max}$ 50, $\dot{V}_{max}$ 30, T_{CO} and sGaw were unchanged throughout the study, as compared to their control values (Table 5A). The chest x-rays were normal at 1 month and 3 months, but at 6 months showed a faint shadow in the left upper lobe (+) which was still there at 9 months and returned back to normal at 12 months (Table 5A, Figure 47). The ECG showed first degree heart block (1^{o}H.B.) in the control study, which persisted through all the study and, in addition, at 1 month T wave was inverted in V_1, at 3, 6 and at 9 months T inverted also in avL and in V_{1-5}, but at 12 months slight improvement occurred in that the T wave was flat in aVL and T inverted in V_{1-3}. The regional lung function for $\dot{Q}/E$% (Table 5B), $\dot{V}$% (Table 5C), $\dot{V}/E$% at 0.2 L/sec (Table 5D) and $\dot{V}/E$%

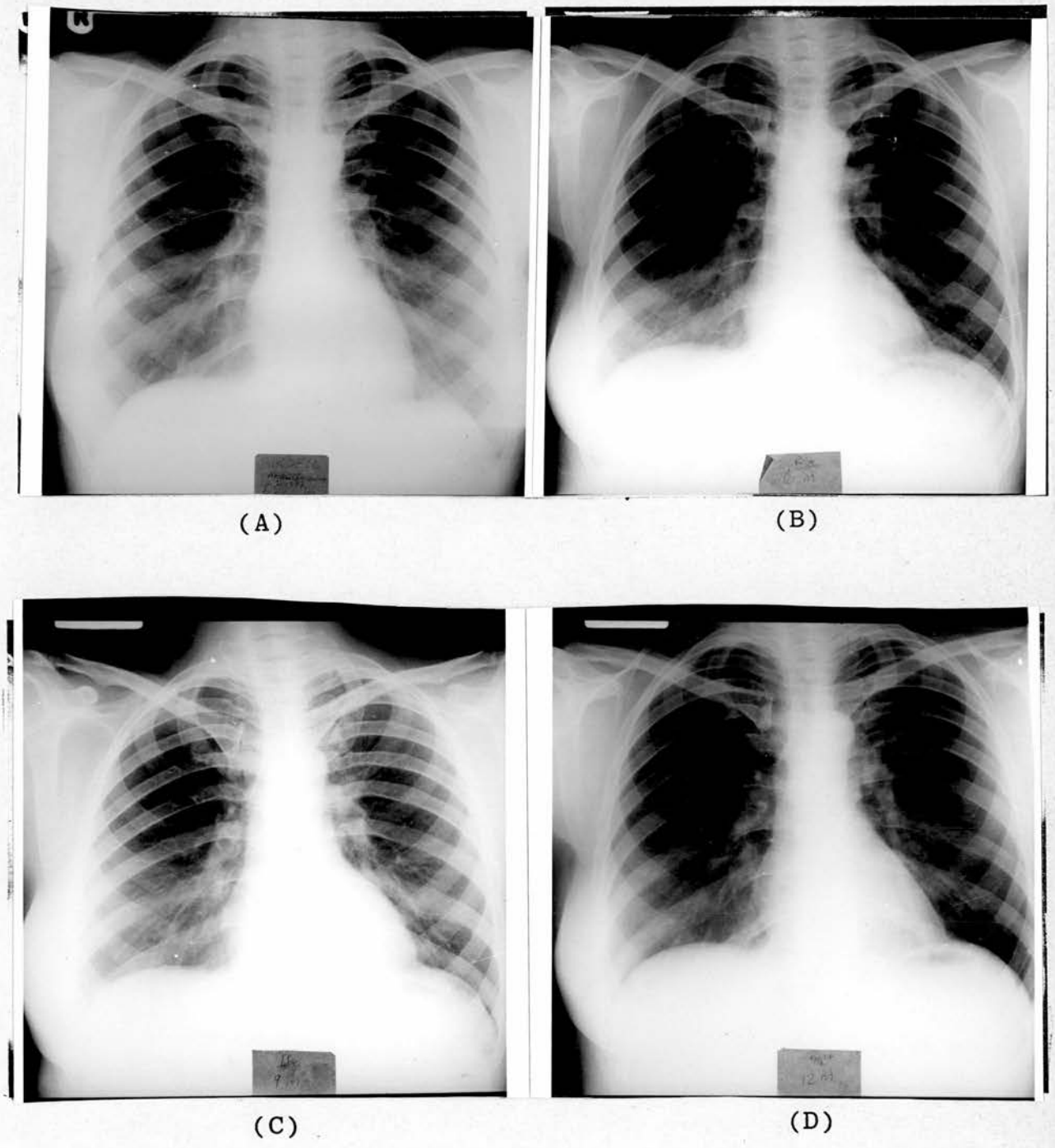


Figure 47

The chest x-rays of patient 4: was normal at "control" study (A); had a faint shadow in the left upper lobe at 6 months (B) and at 9 months (C); and returned back to normal at 12 months (D).

at 1.5 L/sec (Table 5E) were calculated, together with the differences between the irradiated and the non-irradiated 8 horizontal lung segments.

The average of the upper 3 segments for $\dot{Q}$/E% of each lung was calculated, together with the difference between the average of the irradiated lung and that of the non-irradiated lung (Table 13) and these differences plotted against time following radiotherapy (Figure 38). The $\dot{Q}$/E% reduced in the irradiated lung at 1 month, 6 months and 12 months, as compared to the control $\dot{Q}$/E%.

The V% average of the upper 3 segments for each lung and the differencesare shown in Table 14 and again these differences were plotted against time (Figure 39), which showed no significant change in V% of the irradiated lung, as compared to the non-irradiated lung.

The $\dot{V}$/E% at 0.2 L/sec and at 1.5 L/sec average of the upper 3 segments for each lung and the differences between the irradiated and the non-irradiated lung (Tables 15,16) showed reduction in the irradiated $\dot{V}$/E% at the 3 months study, which returned back to normal thereafter (Figures 40,41).

Patient 5

This 59 year old woman had stage II adenocarcinoma of the left breast treated with simple mastectomy and radiotherapy. The minimum radiation dose to the left lung apex was 4150 rads. She was a non-smoker; her height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements,

ECG and chest x-ray findings, which were normal. Following radiotherapy (Tables 12,6A) this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC did not change through all the study, neither did her RV, FEV_1 and all the other parameters of the overall lung function (Table 6A). The chest x-ray was normal at 1 month. However, at 3 months and 6 months it showed slight streaky opacity in the left upper lobe (+), which returned to normal at 9 months and 12 months (Table 6A). The ECG was normal at 1 month and 3 months. However, at 6 months and 9 months it showed T wave inversion (↓) in V_1-V_5, which returned to normal at the 12 months study (Table 6A). The regional lung function for each variable ($\dot{Q}/E\%$, V%, $\dot{V}/E\%$ at 0.2 L/sec and $\dot{V}/E\%$ at 1.5 L/sec) in 8 horizontal lung segments are shown in Tables 6B,6C,6D,6E. Data for the 9 months study were not available due to a technical fault in the videotape recording system. The averages of the upper 3 segments of the irradiated lung and those of the non-irradiated lung, and the differences between them, for each variable are shown in Tables 13,14,15,16.

In each patient analysis of variance was performed to compare the data of the upper 3 segments of each lung with the lower 5 segments of that lung in each parameter. In this patient it was found that the perfusion in the upper part of each lung was greater than that of the lower part of that lung through all the study, with the exception of the data at 12 months. At the 12 months study, for example, the $\dot{Q}/E\%$ in the upper 3 segments of the irradiated lung was (-68.66%), i.e. less than those of

the lower 5 segments of that lung and the $\dot{Q}/E\%$ of the upper 3 segments of the non-irradiated lung was (-67.12%), less than the lower 5 segments of that lung. However, the data at the control study showed that the $\dot{Q}/E\%$ of the irradiated lung was 23.6% greater than those of the lower 5 segments of that lung and the $\dot{Q}/E\%$ of the upper 3 segments of the non-irradiated lung was 40.87% greater than those of the lower 5 segments of that lung. These results would imply that the normal gravitational apex to base gradient of perfusion down the lung was inverted, and are thus open to grave suspicion. Therefore malpositioning of the patient before the gamma camera was suspected. On checking the polaroid film of the count image during the 12 months study and comparing it with those taken at control (Figure 48), 1 month, 3 months and 6 month studies, it was apparent that the apices of both lungs were excluded in these studies. Therefore all the regional data of this patient were excluded in the calculation of the mean values in both tables and figures.

Patient 6

This 47 year old woman had stage I mucoid carcinoma of the left breast treated with simple mastectomy. After one year's observation she developed metastases in the mastectomy scar and was then treated with a course of radiotherapy (Duncan, Forrest, Gray, Hamilton, Langlands, Prescott, Shivas and Stewart, 1975). The minimum radiation dose to the left lung apex was 4190 rads. She was a non-smoker; height, weight, haemoglobin and WBC

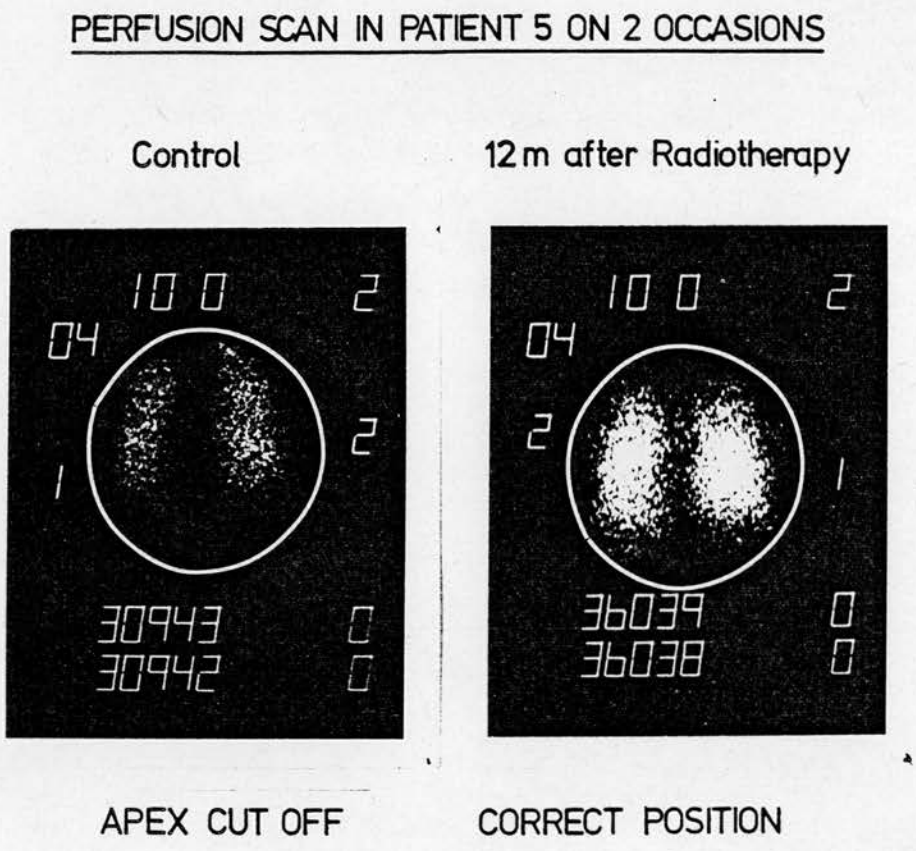


Figure 48

Two polaroid films showing perfusion scan taken at the control study (left) and at 12 months study (right) in patient 5. The apices of both lungs are excluded from the field of the gamma camera in the control study, whereas they were included in the field at the 12 months study.

count are shown in Table 1, together with her overall and regional lung function measurements, ECG and chest x-ray at the control study, which were all normal. Following radiotherapy (Tables 12,7A) this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC was reduced by 1.02 litres at 6 months and by 1.38 litres at 12 months; yet these values were still within her predicted normal ranges (predicted $\pm$ 2 x S.D.). Her RV was reduced by 0.67 litres at 6 months and by 1.23 litres at 12 months; these values were also within her predicted normal ranges. Her T_{CO} (Table 7A) was reduced by 1.36 mmol/min/kPa at 12 months, still within her predicted normal range. All the other measurements of the overall lung function were unchanged. Her chest x-ray was normal at 1 month, 3 months and 6 months, but there was a slight hazy opacity in the upper lobe at 9 months, which was still present at 12 months (+) (Table 7A). The ECG showed T wave inversion in V_{1-2-3} as early as 1 month after radiotherapy and this persisted through all the study. In addition, at 6 months, 9 months and 12 months T wave was inverted also in V_{4-5} (Figure 49). The regional lung function for the variables $\dot{Q}/E\%$ (Table 7B), V% (Table 7C), $\dot{V}/E\%$ at 0.2 L/sec (Table 7D) and $\dot{V}/E\%$ at 1.5 L/sec (Table 7E) were calculated together with the differences between the irradiated and the non-irradiated 8 horizontal lung segments.

The averages of the upper 3 segments in the irradiated and the non-irradiated lungs, together with their differences, are shown in Table 13 for $\dot{Q}/E\%$, Table 14 for V%, Table 15 for $\dot{V}/E\%$ at 0.2 L/sec and in Table 16 for $\dot{V}/E\%$

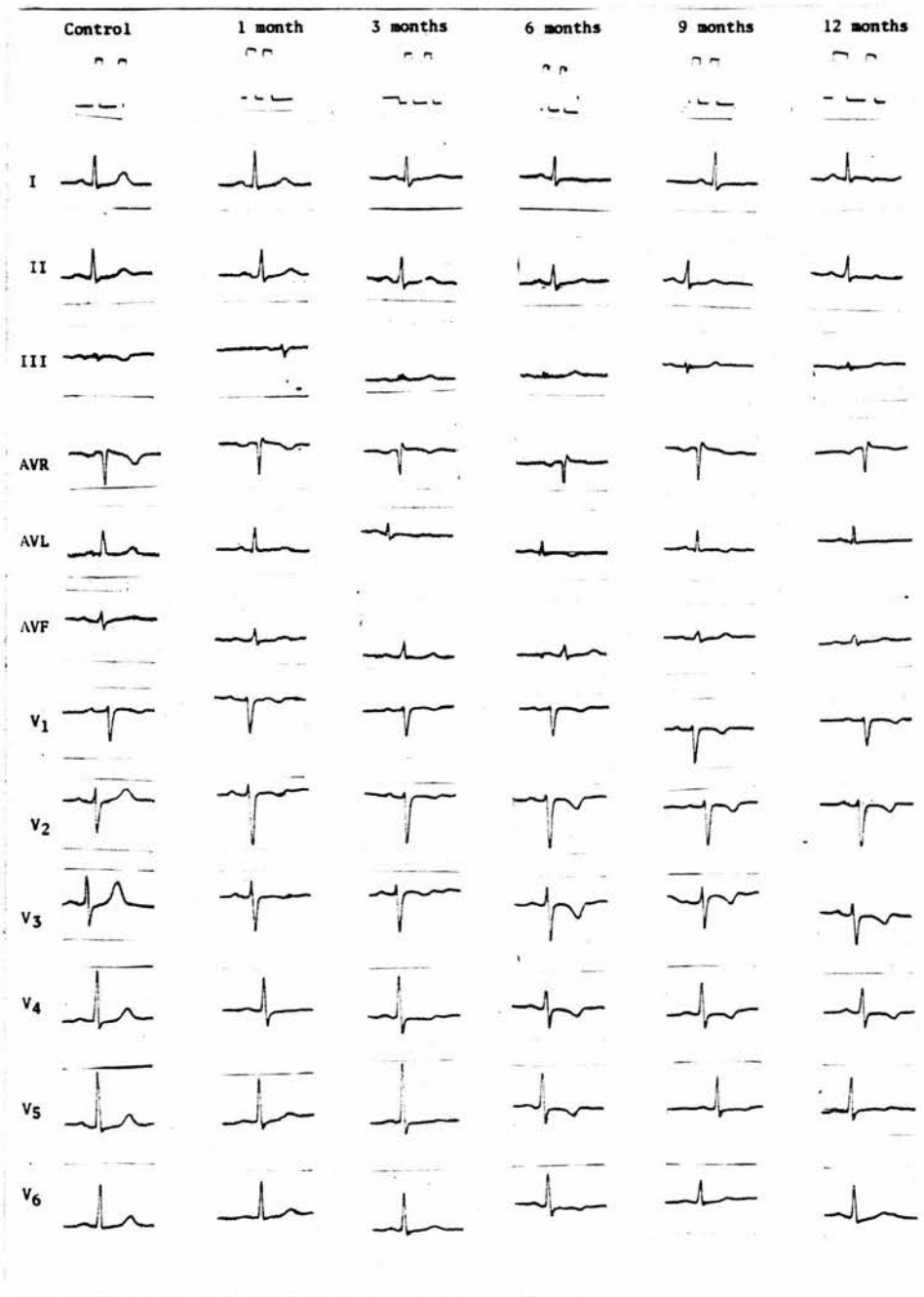


Figure 49

The ECGs (standard 12 leads) of patient 6, at the "control" study and subsequently at 1, 3, 6, 9 and 12 months after radiotherapy. T wave inversion in the anterior chest leads after radiotherapy.

at 1.5 L/sec. The irradiated lung showed reduction in $\dot{Q}/E\%$ at 1 month, which returned back to normal thereafter (Figure 38). The difference in the averages of V% did not change throughout the study (Figure 39). The $\dot{V}/E\%$ at 0.2 L/sec in the irradiated lung decreased at 1 and 3 months, returned to normal at 6 months and decreased again thereafter (Figure 40), whereas $\dot{V}/E\%$ at 1.5 L/sec increased in the irradiated lung, as compared to the non-irradiated lung at 6 months and returned back to normal thereafter (Figure 41).

Patient 7

This 57 year old woman had stage II invasive carcinoma of the right breast treated with simple mastectomy and radiotherapy. The minimum radiation dose to the right lung apex was 3910 rads. She was an ex-smoker; height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements, ECG and chest x-ray at the control study. Her RV in the control study was greater than her predicted normal range (i.e. predicted $\pm$ 2 x S.D.), whereas her FVC and T_{CO} were below the predicted normal ranges for a woman of her age and height. Following radiotherapy (Tables 12,8A) this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC reduced by 0.64 litres at 6 months and by 0.5 litres at 12 months; yet these values were within her predicted normal range (predicted $\pm$ 2 x S.D.). The RV values also reduced by 0.48 litres at 6 months and by 0.32 litres at 12 months. Moreover, her FEV_1 was

reduced by 0.45 litres at 6 months and the same reduction persisted throughout at 9 months and 12 months. This reduction meant that her FEV_1 fell to below the predicted normal range in this patient. All the other values of the overall lung function were unchanged through all the study (Table 8A). The chest x-ray was normal at 1 month and 3 months. However, at 6 months, 9 months and 12 months there was a slight opacity (+) in the right upper lobe (Table 8A). The ECGs were normal throughout the study. The regional lung function for each variable ($\dot{Q}$/E%, V%, $\dot{V}$/E% at 0.2 L/sec and $\dot{V}$/E% at 1.5 L/sec) in 8 horizontal lung segments are shown in Tables 8B,8C,8D,8E. The averages of the upper 3 segments of the irradiated lung and those of the non-irradiated lung, and the differences between them for each variable are shown in Tables 13,14, 15,16. In this patient also, analysis of variance showed that perfusion in the upper part of the lung was greater than that in the lower part of the lung and for the reasons discussed earlier, it was concluded that malpositioning of the patient was present in both the control study and the 3, 6, and 9 month studies. Malpositioning was confirmed on checking the polaroid films taken at the time of the study. Thus the regional data of this patient was also excluded in the calculation of the means and values in both tables and figures.

Patient 8

This 50 year old woman had stage II scirrhous carcinoma of the right breast treated with simple mastectomy and

radiotherapy. The minimum radiation dose to the right lung apex was 4115 rads. She was a non-smoker; height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements, ECG and chest x-ray at the control study, which were all normal. Following radiotherapy (Tables 12,9A) this patient was studied at 1, 3 and 6 months only as the patient developed metastases in her liver after this period. Her TLC was reduced by 0.42 litres at 6 months, although still within her predicted normal ranges (predicted $\pm$ 2 x S.D.). Her RV was reduced by 0.2 litres at 6 months. All the other variables of overall lung function were unchanged, except T_{CO} which was reduced by 1.43 mmol/min/kPa at 3 months and by 1.86 mmol/min/kPa at 6 months; yet it was still within her predicted normal range (Table 9A). The ECGs were normal throughout the study. Chest x-ray, on the other hand, was normal at 1 month, but showed a slight opacity (+) in the right upper lobe at both the 3 month and at the 6 month studies (Table 9A). The regional lung function of the variables $\dot{Q}/E\%$ (Table 9B), V% (Table 9C), $\dot{V}/E\%$ at 0.2 L/sec (Table 9D) and $\dot{V}/E\%$ at 1.5 L/sec (Table 9E) were calculated, together with the differences between the irradiated and the non-irradiated 8 horizontal lung segments.

The averages of the upper 3 segments in the irradiated and the non-irradiated lungs, together with their differences are shown in Table 13 for $\dot{Q}/E\%$, Table 14 for V%, Table 15 for $\dot{V}/E\%$ at 0.2 L/sec and in Table 16 for $\dot{V}/E\%$ at 1.5 L/sec. The average $\dot{Q}/E\%$ of the upper 3 segments of the irradiated

lung showed progressive reduction at 1 month, 3 months and 6 months, as compared to the average of the upper 3 segments of the non-irradiated lung (Figure 38). The V% was almost unchanged through all the study (Figure 39). The $\dot{V}$/E% at 0.2 L/sec showed reduction in the irradiated upper lung at 3 months and 6 months (Figure 40). However, the $\dot{V}$/E% at 1.5 L/sec was greater in the irradiated lung apex at 3 months and 6 months, as compared to those of the non-irradiated side (Figure 41).

Patient 9

This 42 year old woman had stage I scirrhous carcinoma of the left breast treated with simple mastectomy and radiotherapy. The minimum radiation dose to the left lung apex was 4000 rads. She was a non-smoker; height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements, ECG and chest x-ray at the control study, which were all normal. Following radiotherapy (Tables 12,10A) this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC was reduced by 0.77 litres, 0.69 litres, 0.37 litres, 0.71 litres and 0.05 litres at 1 month, 3 months, 6 months, 9 months and 12 months respectively. These values were within the predicted normal ranges for this patient (predicted $\pm$ 2 x S.D.). Her RV fell by 0.58 litres at 9 months, which was below her predicted normal range and returned back to normal at 12 months (Table 10A). All the other variables of the overall lung function were unchanged through all the study. The chest x-rays were

normal and unchanged throughout the study (Table 10A). The ECGs showed T wave inversion (↓) in V_2-V_6, 3 months after radiotherapy, which persisted throughout the study (Table 10A). The regional lung function for the variables $\dot{Q}/E\%$ (Table 10B), V% (Table 10C), $\dot{V}/E\%$ at 0.2 L/sec (Table 10D) and $\dot{V}/E\%$ at 1.5 L/sec (Table 10E) were calculated together with the differences between the irradiated and the non-irradiated 8 horizontal lung segments.

The averages of the upper 3 segments in the irradiated and the non-irradiated lungs, together with their differences are shown in Table 13 for $\dot{Q}/E\%$, Table 14 for V%, Table 15 for $\dot{V}/E\%$ at 0.2 L/sec and in Table 16 for $\dot{V}/E\%$ at 1.5 L/sec. The average $\dot{Q}/E\%$ of the upper 3 segments of the irradiated lung was greater than that of the non-irradiated lung at the control study. However, at 6 months the average in the irradiated upper lung fell and returned back at 9 months; whereas at 12 months this average in the irradiated lung fell and showed less perfusion than the non-irradiated lung (Table 13, Figure 38). The average V% did not change throughout the study (Figure 39). The $\dot{V}/E\%$ at 0.2 L/sec increased at 3 months, returned to the control level at 6 months, but showed reduction in the irradiated upper lung at 12 months (Figure 40). The $\dot{V}/E\%$ at 1.5 L/sec increased in the irradiated upper lung at 3 months and gradually decreased thereafter (Figure 41).

Patient 10

This 35 year old woman had a stage I intraduct carcinoma of the left breast treated with simple mastectomy. After one year's observation she developed lymph node metastases and was therefore treated with a course of radiotherapy at that time (Duncan et al, 1975). The minimum radiation dose to the left lung apex was 4135 rads. She was a non-smoker; height, weight, haemoglobin and WBC count are shown in Table 1, together with her overall and regional lung function measurements, ECG and chest x-ray at the control study, which were all normal. Following radiotherapy (Tables 12,11A) this patient was studied at 1, 3, 6, 9 and 12 months. Her TLC was reduced by 0.41 litres at 6 months and at 9 months; whereas at 12 months it was reduced by 0.34 litres. These values were around the lower limit of her predicted normal ranges (predicted $\pm$ 2 x S.D.). The RV was not changed throughout the study and all other lung volumes were likewise unchanged (Table 11A). The T_{CO}, on the other hand, was reduced by 1.33 mmol/min/kPa at 3 months, but returned to around the control value thereafter (Table 11A). The chest x-ray was normal at 1 month, 3 months and 6 months. However, at 9 and 12 months the chest x-rays showed slight opacity (+) in the left upper lobe (Table 11A). The ECGs showed a biphasic T wave in V_2 at 1 month and at 3 months the T wave was also flat in V_{1-5}, which then persisted throughout the study (Table 11A).

The regional lung function for the variables $\dot{Q}/E\%$

(Table 11B), V% (Table 11C), $\dot{V}$/E% at 0.2 L/sec (Table 11D) and $\dot{V}$/E% at 1.5 L/sec (Table 11E) were calculated together with the differences between the irradiated and the non-irradiated 8 horizontal lung segments.

The averages of the upper 3 segments in the irradiated and the non-irradiated lungs, together with their differences are shown in Table 13 for $\dot{Q}$/E%, Table 14 for V%, Table 15 for $\dot{V}$/E% at 0.2 L/sec and in Table 16 for $\dot{V}$/E% at 1.5 L/sec. The average $\dot{Q}$/E% of the upper 3 segments of the irradiated lung was reduced progressively at 3 months and at 6 months; it returned to normal at 9 months (Figure 38).

The average V% did not change through all these studies (Figure 39). The $\dot{V}$/E% at 0.2 L/sec was reduced at 1 month and 3 months, but returned to around normal thereafter (Figure 40). The $\dot{V}$/E% at 1.5 L/sec increased at 6 months and returned to normal thereafter (Figure 41).

4. Summary

In these 10 women the radiotherapy affects the total and regional lung function (Figures 36-41), in the following manner:

i. It caused significant reduction in the total lung capacity (TLC) without changing the vital capacity (VC). This TLC reduction was mainly due to the significant reduction in residual volume (RV). Thus, radiotherapy caused a restrictive defect (Figure 37).

ii. No effect was detected on the airways of the lung since the sGaw (a test for large airway function) and

$\dot{V}_{max}$ 50 and $\dot{V}_{max}$ 30 (tests for small airway function) showed no change after radiotherapy (Figure 36).

iii. T_{CO} (a test for ventilation-diffusion and perfusion function) was unchanged after radiotherapy (Figure 36).

iv. Comparison of regional ventilation at slow flow rate, between the irradiated lung and the non-irradiated "control" lung, in the upper 3 segments, showed no changes, either before radiotherapy or sequentially at 1, 3, 6, 9 and 12 months after radiotherapy (Figure 40). However, regional ventilation at higher flow rate showed less ventilation in the treated side before radiotherapy, but showed significantly higher ventilation at 6 months, as compared to the pre-radiotherapy value, and was still higher at the 12 months study (Figure 41).

v. There was a signficant reduction in perfusion of the upper zone of the irradiated lung corresponding to the region receiving the radiotherapy. These perfusion changes were significant as early as 1 month after radiotherapy (Figure 38), and returned back to normal at 9 months in some patients, as detected by radio-active Xe^{133} studies. These perfusion reductions were confirmed by lung scan at 12 months for each patient using Tc^{99m} macroaggregated albumin.

vi. There were no consistent radiological changes in most of these patients.

vii. ECGs showed T wave changes in those patients who had their radiotherapy to the left side.

ii) Cross-sectional Study

The measurements in this study were made on one occasion only in each patient. The 48 women studied had had simple mastectomy and radiotherapy for their breast cancer between 1 and 14 years previously (Figure 50). These women were divided into two groups; those without changes in the chest x-ray (Table 17) and those with radiological changes attributed to the radiotherapy (Table 18).

1. Results of the overall and regional lung function in the first group (i.e. with no radiological changes

The number of women studied in this group was 23 and they were studied once between 1 and 14 years after radiotherapy (Table 17, Figure 50). The age range of the patients in this group was between 42-73 years (Figure 51). Ten patients were non-smokers, 2 were ex-smokers and the rest were smokers. The height, weight, haemoglobin, WBC count, histopathological diagnosis and the stages for each individual patient in this group are shown in Table 17. The minimum radiation dose to the irradiated lung apex ranged between 3760 and 4340 rads (Table 17). The irradiated side was on the left in 9 women and on the right in the rest of this group (Table 17). The ECGs showed T wave changes in 7 out of the 9 patients in whom the radiotherapy was to the left breast. None of the patients who received radiotherapy to the right breast showed any T wave changes in the ECG (Table 17). As mentioned before, this group showed no radiological changes in their chest x-rays.

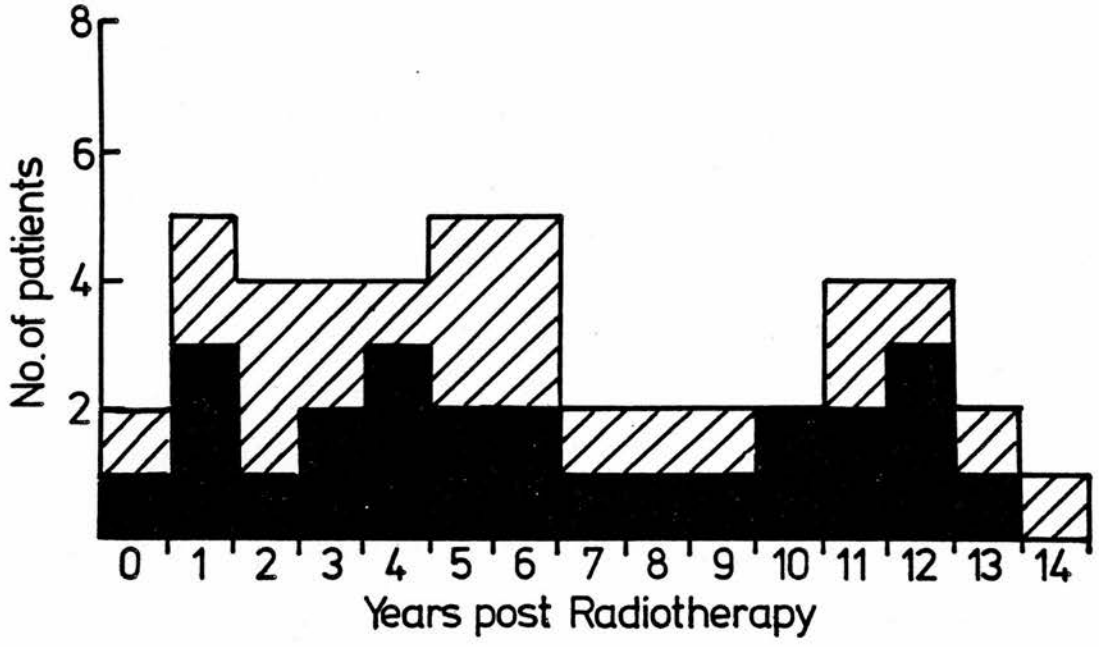


Figure 50

Forty-eight women studied once between 1-14 years after radiotherapy for breast cancer.

▨ those with no radiological changes

■ those with radiological changes

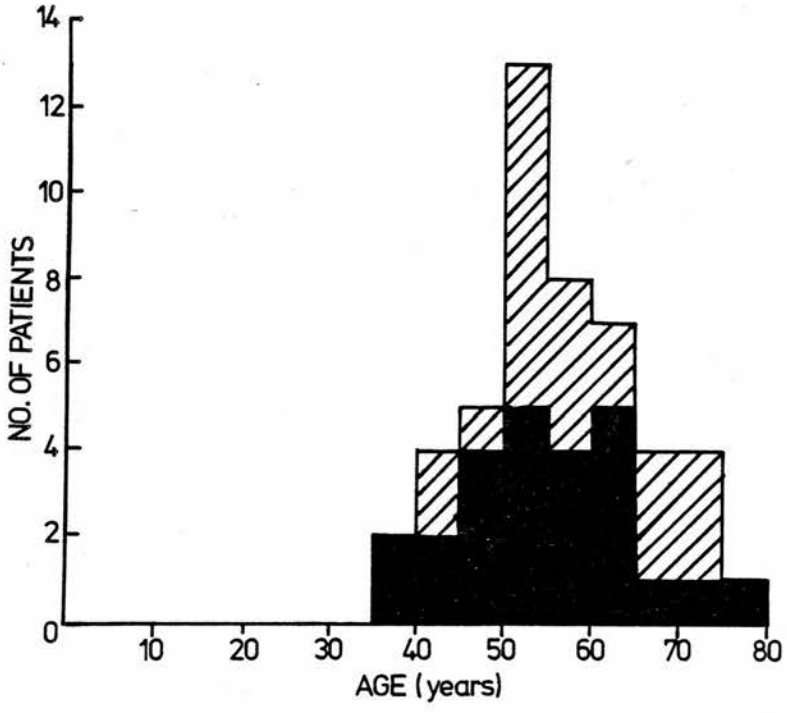


Figure 51

The age distribution of 48 women studied once between 1-14 years after radiotherapy for breast cancer.

▨ those with no radiological changes

■ those with radiological changes

The overall lung function measurements, together with the regional lung function measurements for each individual patient, with the means and standard errors, are shown in Table 17. The static and dynamic lung volumes and T_{CO} were also expressed as a percentage of the predicted normal values (Table 17). The TLC% predicted in these patients were distributed around 100% predicted, with a mean value of 100 $\pm$ 3.9% and thus were normal for these patients (Figure 52). Moreover, the RV% predicted for these patients are shown in Figure 53, all except 6 patients, had RV values of less than 100%. Furthermore, the FEV_1% predicted showed that these patients had a normal FEV_1 with a mean value of 111 $\pm$ 3.5% (Table 17, Figure 54). However, the T_{CO}, expressed as a percentage of the predicted normal values for these women, was below 100% in all but 2 patients with a mean value of 76 $\pm$ 3.7% (Table 17, Figure 55). In 6 of these women, the T_{CO}% was below 2 S.D. of the predicted normal value for such women.

On the other hand, the regional lung function measurements [perfusion/unit alveolus% ($\dot{Q}/E$%), ventilation/unit alveolus at 0.5 L/sec ($\dot{V}/E$%) and lung volume (V%)] showed that the average value of perfusion per alveolus ($\dot{Q}/E$%) of the upper 3 segments of the irradiated lung was less than the average of the upper 3 segments of the non-irradiated lung, the differences between these averages being shown in Table 17, Figure 56. The mean reduction in perfusion/alveolus of the irradiated upper lung was -13.1 $\pm$ 3.2%. This reduction of $\dot{Q}/E$% in the irradiated lung was highly significant ($P < 0.005$), using Wilcoxon's rank test for paired difference.

However, the average regional volume (V%) of the upper 3 segments in the irradiated lung was not significantly different from that of the same 3 segments in the non-irradiated lung, the differences between these averages for each patient being shown in Table 17, Figure 57, with a mean difference of 0.12 ± 0.15%.

Furthermore, the $\dot{V}$/E% average of the upper 3 segments in the irradiated lung was also not significantly different from those of the non-irradiated lung, and the difference between these averages for each patient are shown in Table 17, Figure 58, with a mean difference of 1.9 ± 2.6%.

2. Results of the overall and regional lung function in the second group (i.e. with radiological changes

The number of women studied in this group was 25. They were also studied once between 1 and 14 years after radiotherapy (Table 18, Figure 50). The age range of the patients in this group was between 36-75 years (Table 18, Figure 51). The age, smoking history, height, weight, haemoglobin, WBC count, histopathological diagnosis and the clinical staging of the breast cancer in each patient are shown in Table 18. The minimum radiation dose to the irradiated lung apex ranged between 3480 and 4260 rads (Table 18). The irradiated side was on the right in 15 patients and on the left in the rest (Table 18).

The ECGs were normal in most of the patients and only 4 out of 10 patients who had their radiotherapy to the left side showed some T wave inversion in the chest leads (Table 18).

The chest x-ray changes, on the other hand, were graded without knowledge of physiological findings, according to the severity of the radiological changes alone and

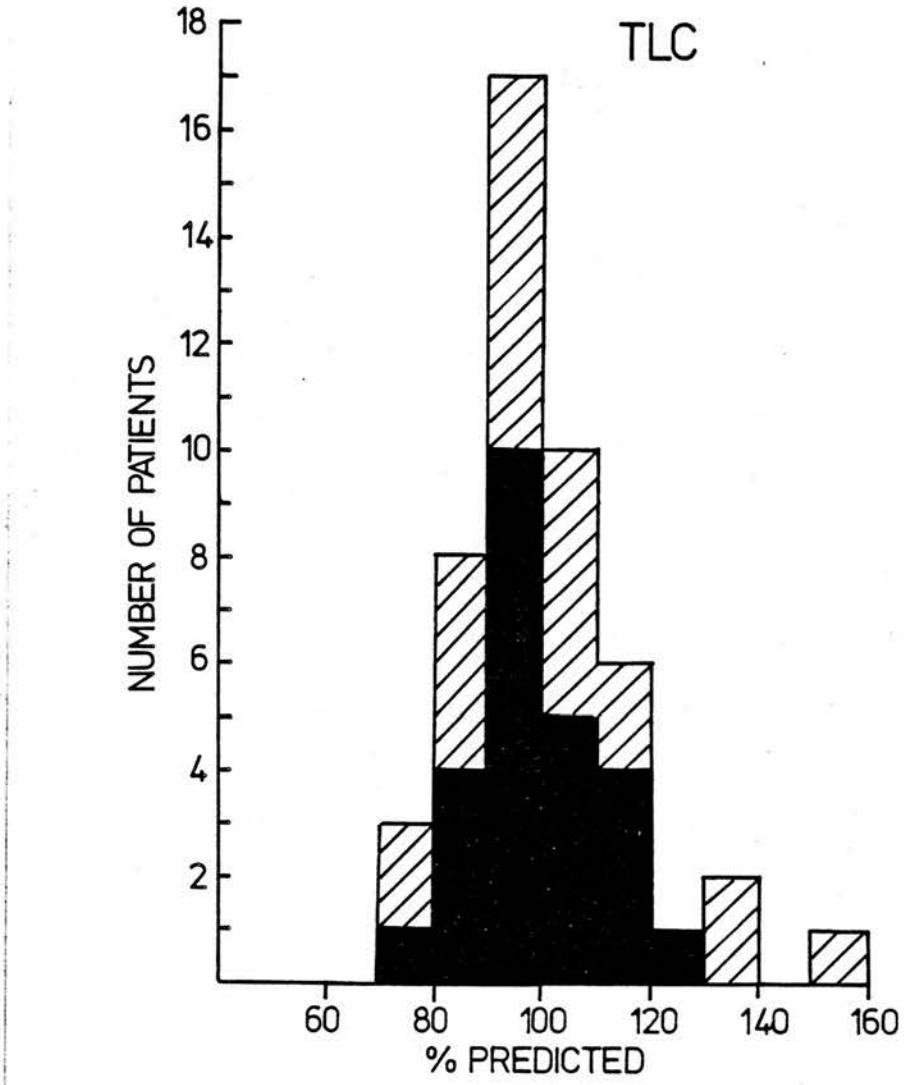


Figure 52

The total lung capacity as % predicted in 48 patients studied once between 1-14 years after radiotherapy.

▨ those with no radiological changes

■ those with radiological changes

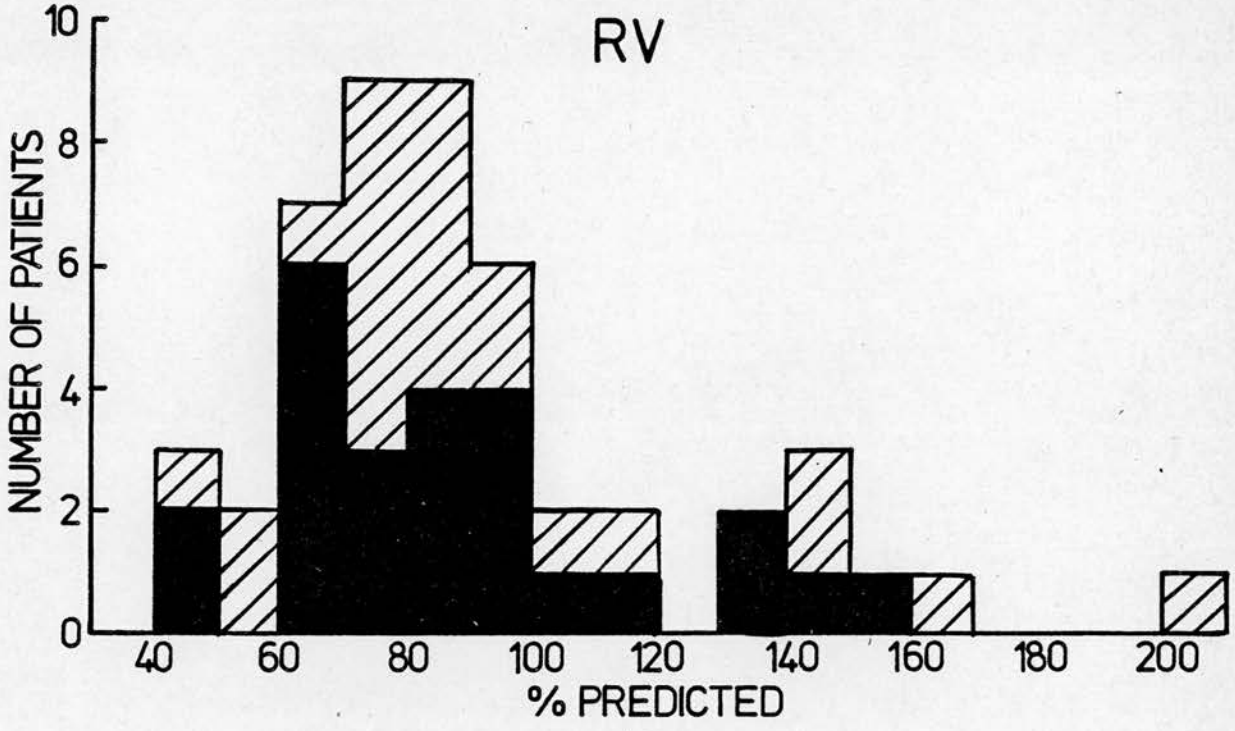


Figure 53

The residual volume as % predicted in 48 patients studied once between 1-14 years after radiotherapy.

▨ those with no radiological changes

■ those with radiological changes

were scored between (+) for slight opacification in the irradiated upper lung, (++) for medium changes in the irradiated lung and (+++) for severe changes in the irradiated lung (Table 18).

The overall and regional lung function measurements for the individual patients in this group, together with the means and standard errors, are shown in Table 18. The TLC, VC, RV, RV/TLC%, FEV_1, FVC, FEV_1/FVC and T_{CO} were expressed also as a percentage of the predicted normal values (Table 18). The TLC, as a percentage of the predicted normal value in these patients, was normally distributed around 100%, with a mean value of 99 $\pm$ 2.2% and was thus normal for these patients (Figure 52). Furthermore, the RV% predicted for these patients are shown in Figure 53, all but 6 patients showed values below 100% predicted. The FEV_1% predicted was below the normal range in 2 patients; otherwise it was higher than 100% of the predicted normal value in 19/25 of the patients in this group, with a mean value of 110 $\pm$ 4.29% (Table 18, Figure 54).

On the other hand, the T_{CO}, as a percentage of the predicted normal value (Table 18, Figure 55), was below 100% in all but 2 patients, with a mean value of 75 $\pm$ 2.61%, and in 5 patients it was below the normal ranges for these patients (i.e. predicted $\pm$ 2 x S.D.).

However, the regional lung function measurements of $\dot{Q}$/E%, $\dot{V}$/E% and V% showed almost the same results as in the first group of patients, who did <u>not</u> show radiological changes. The average value for $\dot{Q}$/E% for the upper 3

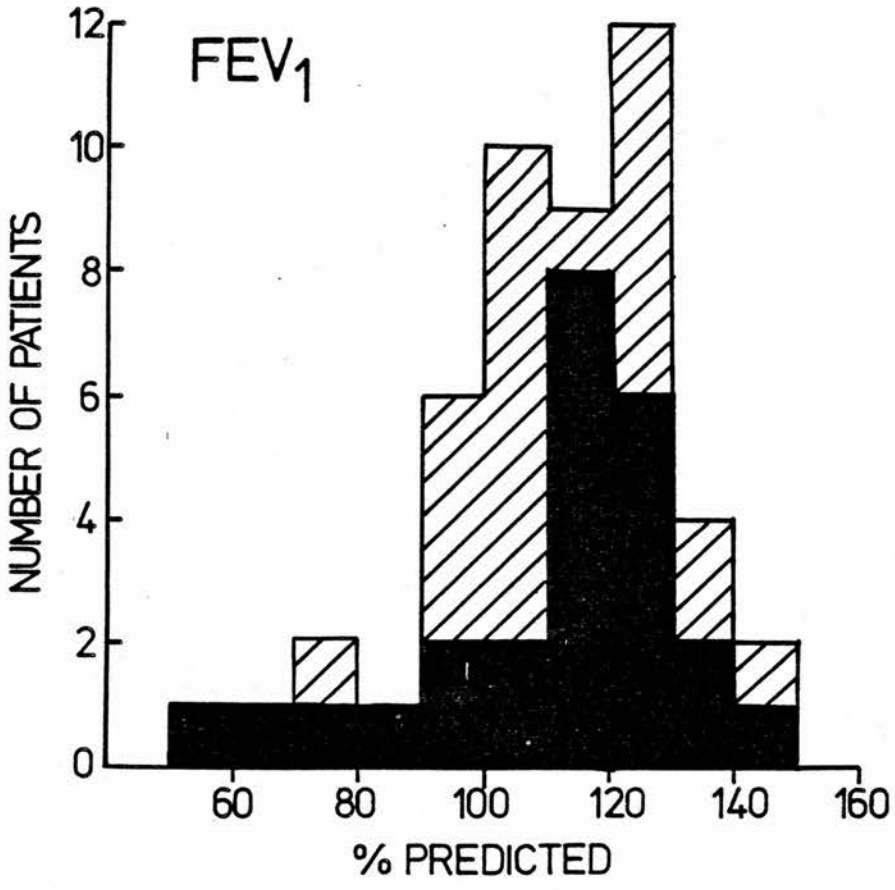


Figure 54

The forced expiratory volume at 1.0 sec as % predicted in 48 patients studied once between 1-14 years after radiotherapy.

▨ those with no radiological changes

■ those with radiological changes

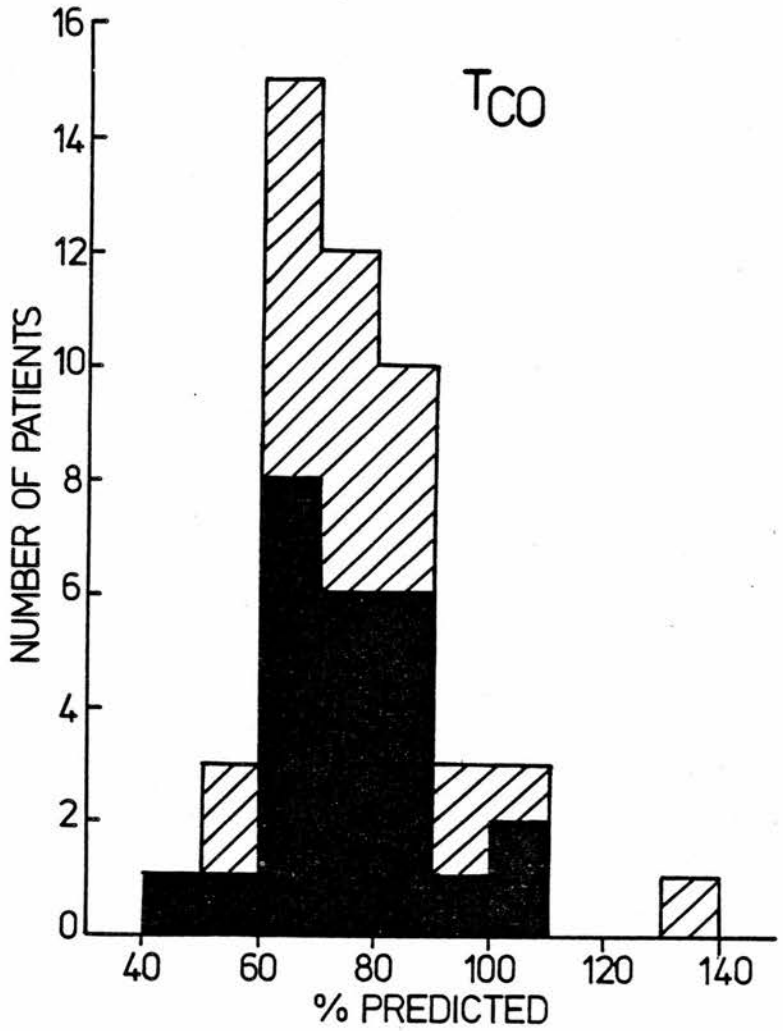


Figure 55

The transfer factor for carbon monoxide (T_{CO}) as % predicted in 48 patients studied once between 1-14 years after radiotherapy.

▨ those with no radiological changes

■ those with radiological changes

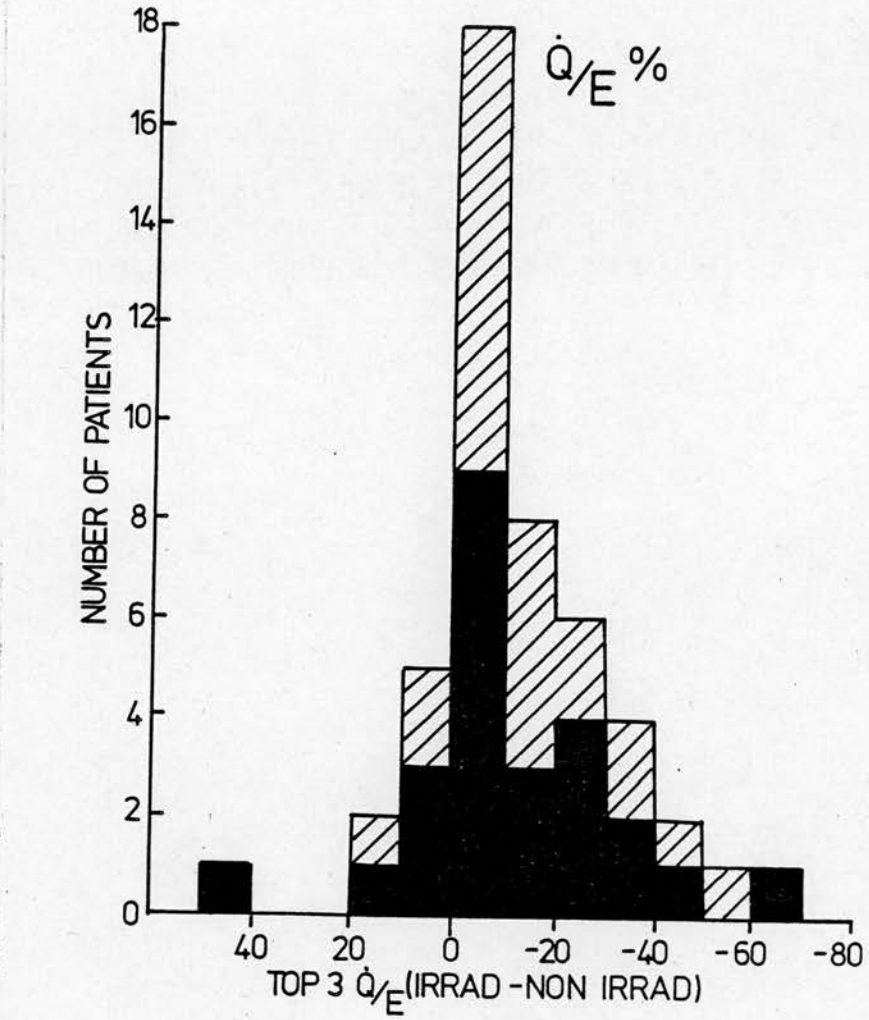


Figure 56

The perfusion/alveolus % calculated as the difference between the average value of the upper 3 segments of the irradiated lung and that of the non-irradiated lung in 48 patients studied once between 1-14 years after radiotherapy for breast cancer.

▨ those with no radiological changes

■ those with radiological changes

There was highly significant reduction ($P < 0.005$) in the upper zones of the irradiated lung, as compared to those of the non-irradiated lung in both groups.

segments in the irradiated lung was less than that of the non-irradiated lung and the differences between these averages, with a mean reduction of -11.8 ± 4.2% (Table 18, Figure 56) was highly significant ($P < 0.005$), using Wilcoxon's rank test for paired differences. Furthermore, the V% average of the upper 3 segments in the irradiated lung was not significantly different from the average of the upper 3 segments in the non-irradiated lung. The differences between these averages was normally distributed around zero% difference, with a mean difference of 0.04 ± 0.15% (Table 18, Figure 57).

Moreover, the $\dot{V}/E$% average of the upper 3 segments in the irradiated lung was not significantly different from that of the non-irradiated lung. The differences between these averages are shown in Table 18 and Figure 58, which shows that the $\dot{V}/E$% differences of averages are distributed normally around zero%, with a mean difference of 1.25 ± 2.3%.

3. Summary

Both these groups of patients in the cross-sectional study (with or without radiological changes attributable to radiotherapy) showed normal overall lung function (i.e. within the predicted normal values for women with similar age and height to these patients). However, only T_{CO} was on the lower side. On the other hand, regional lung function measurements in both groups showed significant ($P < 0.005$) reduction in the regional distribution of perfusion in the upper region of the irradiated lung, as compared to that of the non-irradiated lung. However, there was no

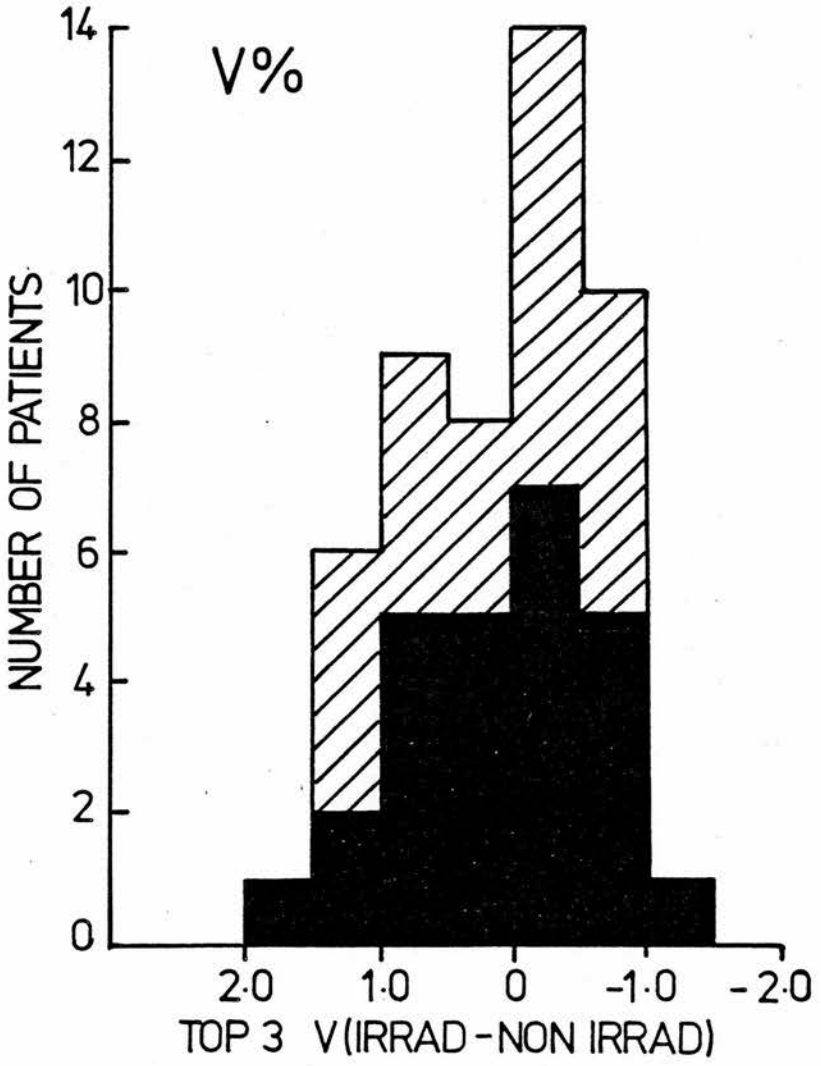


Figure 57

The lung volume % calculated as the difference between the average value of the upper 3 segments of the irradiated lung and that of the non-irradiated lung in 48 patients studied once between 1-14 years after radiotherapy for breast cancer.

▨ those with no radiological changes

■ those with radiological changes

There was no signficant difference between the upper zones of the 2 lungs in both groups.

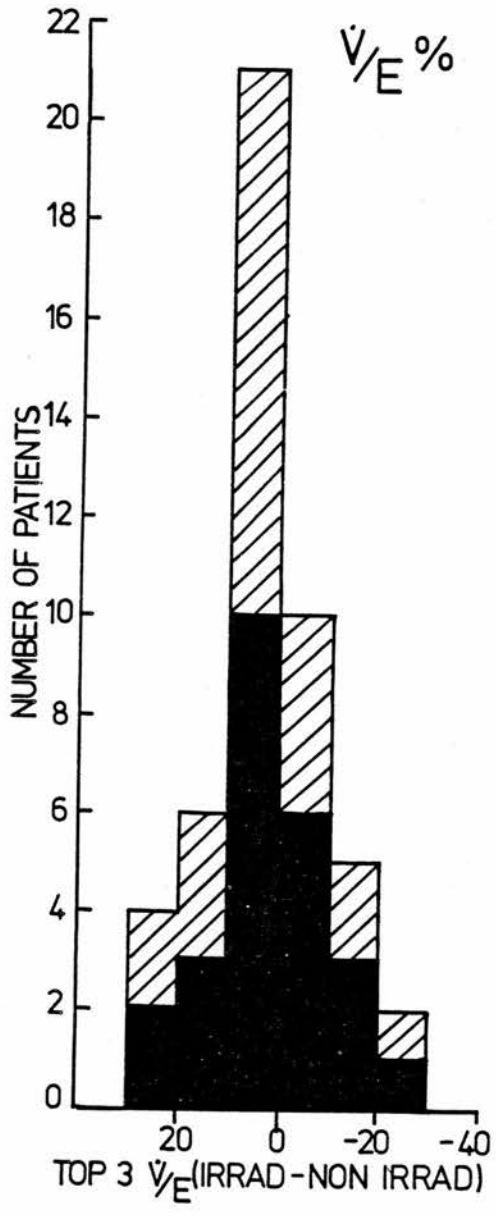


Figure 58

The ventilation/alveolus % calculated as the difference between the average value of the upper 3 segments of the irradiated lung and that of the non-irradiated lung in 48 patients studied once between 1-14 years after radiotherapy for breast cancer.

▨ those with no radiological changes

■ those with radiological changes

There was no significant difference between the upper zones of the 2 lungs in both groups.

significant difference in the regional distribution of ventilation and in lung volume between the upper region of the irradiated lung and that of the non-irradiated lung.

IV DISCUSSION

i) Sequential Study

The present study has demonstrated a variable response to radiotherapy of the lungs in each patient. These responses bore no relation to age, height, weight, smoking history, the total lung capacity (TLC), the forced expiratory volume at 1.0 sec (FEV_1) or the FEV_1/FVC ratio of the patient. They were also not related to the histopathological type, the stage or the side of the carcinoma of the breast. We thus presume that they reflect the degree of damage caused by radiation, and the individual patient's response of lung tissue to that damage. Technical factors, including the quality of radiation, the total dose and the rate at which the total dose was delivered (i.e. the dose, the number of fractions and the time over which the doses were delivered), as well as the volume of the lung tissue irradiated, were kept almost the same in all these patients, so that these potential variables, which were suggested by Gross (1977) as important, cannot account for the variability in response.

1. Overall lung function

The overall lung function measurements showed reduction of the total lung capacity (TLC) after radiotherapy in 8 out of the 10 patients. This reduction was significant ($P < 0.05$) at one month after radiotherapy and was also significant ($P < 0.01$) at 6, 9 and 12 months after radiotherapy, as compared to the control values (Figure 37). This reduction in TLC was mainly due to the

reduction in residual volume (RV) in these patients (Figure 37), as the vital capacity (VC) was not changed by radiotherapy, as compared to control values. The reduction in TLC and RV following radiotherapy is in keeping with the findings of Emirgil and Heinemann (1961) and Prato et al (1977).

The FEV_1, although showing a statistically significant reduction in the mean value at 3, 9 and 12 months, as compared to the mean control value (Figure 37), was only reduced by a very small amount in absolute terms, the maximal reduction in the mean FEV_1, as compared to the control value, being only 0.11 litres, which lies within the standard deviation of the measurements. This minimal change in FEV_1 following radiotherapy is similar to the findings of Prato et al (1977) following radiotherapy with Co^{60} for breast cancer in 25 patients, for they also found no changes in FEV_1. However, in this present study there was no change (statistically or absolute) in VC or FVC following radiotherapy, as compared to the control values in each patient (Figure 36), unlike the findings of Emirgil and Heinemann (1961) and Prato et al (1977).

The $\dot{V}_{max}$ 50 and $\dot{V}_{max}$ 30 showed no change following radiotherapy, as compared to the control values (Figure 36), in keeping with the findings of Prato et al (1977). It has been said (Mead, Turner, Macklem and Little, 1967) that in the lower three-quarters of the vital capacity, maximum expiratory flow rates reflect the dimensions of those airways which lie between the alveoli and the equal pressure points in the intrathoracic airways. This would

imply that the small airways of the lungs were unchanged following radiotherapy.

No change could be detected in the specific airway conductance (sGaw) following radiotherapy, as compared to the control value (Figure 36), which suggests that there was no change in the large airways of the lungs (trachea and major bronchi) which constitute the major part of resistance to air flow in the lungs (Macklem and Mead, 1967).

Transfer factor (T_{CO})

The T_{CO} values showed no significant change following radiotherapy, in a paired comparison with the control value in each patient (Figure 36). However, patient 6 showed a fall in T_{CO} at 9 and 12 months after radiotherapy, as compared with the control value, and in this patient there were also radiological changes (slight hazy opacity), coinciding with the reduction in T_{CO}. Patient 8 also showed reduction in T_{CO} at 3 and 6 months after treatment, which also coincided with changes in the chest x-rays (Table 9A, Figure 59); patient 10 showed reduction in T_{CO} after 3 months, without any radiological changes and the T_{CO} returned to normal in the subsequent studies in this patient. This reduction in T_{CO} in these 3 patients is in keeping with the findings of Emirgil and Heinemann (1961) in their 4 breast cancer patients, who were treated with approximately the same radiation dose over the same period. Similar results were obtained by Voutilainen et al (1962); Brady et al (1965); Germon

(A) (B)

Figure 59

The chest x-ray of patient 8 was normal at the "control" study (A), and had a faint shadow in the right upper lobe at 6 months after radiotherapy (B).

et al (1968); Boushy et al (1970) following radiotherapy in patients with bronchogenic carcinoma. The reduction in T_{CO} in these 3 patients is also in keeping with the results of thoracic irradiation in animals (Sweany et al, 1959; Teates, 1965).

The pathological changes in radiation-induced lung damage in animal studies (Gross, 1977) consisted of thickening and folding of the basement membrane, increase in size and number of type 2 pneumocytes, swelling of capillaries with widespread capillary obstruction due to platelets, fibrin and collagen (Phillips, 1966; Adamson et al, 1970; Phillips et al, 1972), with resultant encroachment on the alveolar spaces (Phillips, Benak and Ross, 1972). These changes will cause a reduction in the diffusing capacity as the alveolar-capillary membrane component (Dm) of the barrier to diffusion, separating the alveolar gas from the haemoglobin molecules in the red cells, will increase in the irradiated region; as:

$$Dm = \frac{Ad}{Y} \qquad \text{(Bates and Christie, 1965)}$$

Where A = the total area of the lung membrane (in cm^2)

d = the diffusion coefficient for unit area and unit thickness (in $ml CO.mm\ Hg^{-1}.Cm^{-2}.Cm^{-1}$)

and y = the average thickness of the membrane (in cm)

Probably of greater importance, the capillary obstruction in the irradiated region will cause some reduction in blood flow ($\dot{Q}$) and thus contribute to the reduction in CO uptake ($\dot{V}_{CO}$), which is considered as a process limited both by

diffusion and flow, as expressed by the following equation:

$$\dot{V}_{CO} = \dot{Q}.\ \beta.\ PA_{CO}\ (1-\exp\ [\frac{-D}{\dot{Q}\beta}])$$ (Piiper and Sikand, 1966)

Where $\dot{Q}$ = blood flow in ml/min

β = the slope of the CO dissociation curve of the blood in mlCO.ml blood^{-1} mm Hg^{-1}

PA_{CO} = the alveolar CO pressure in mm Hg

D = the diffusing capacity

In summary, therefore, the reduction in T_{CO} in patients 6, 8 and 10 was presumed to result from the reduction in Dm, which in turn appears to arise from the radiation damage. However, the other patients showed no change in T_{CO} following radiotherapy (Figure 36). Moreover, the transfer coefficient (K_{CO}) was calculated for all the 10 patients before radiotherapy and at the different intervals after radiotherapy by dividing the T_{CO} by TLC, giving K_{CO} in mmol $min^{-1}kPa^{-1}L^{-1}$. This transfer coefficient increased following radiotherapy, as compared to the control values. This resulted as the T_{CO} did not change in 7/10 of these patients; whereas in all 10 patients the TLC was reduced significantly following radiotherapy. However, the increased K_{CO} was not significant at 6 months after therapy, as compared to the control value, although it was significantly higher ($P < 0.05$) at 9 months and 12 months. This might arise if the T_{CO} in the control study was lower as a result of anaemia following the mastectomy (as anaemia causes

reduction in θ and thus reduction in T_{CO} [Rankin, McNeill and Forster, 1961]), as for example the Hb in patient 9 was 10.8 g/dl at the time of the control study and was 11.8 at the time of the 9 months and 12 months studies; or the T_{CO} after radiotherapy increased due to a training effect. The increased K_{CO} after radiotherapy, as compared to the control value, may be due to increase in the volume of the blood in the other pulmonary capillaries, possibly due to redistribution of blood from the irradiated region to the other areas of the lung.

2. Radiological changes

The chest x-rays in these patients showed either no changes following radiotherapy (patients 1, 2, 3 and 9) or only a very slight hazy opacity in the upper zone of the irradiated lung at 3 and 6 months or at 6 and 9 months after therapy, which thereafter returned to normal in patients 4 and 5. However, in patients 6 and 10 slight chest x-ray changes persisted in the upper zone of the left irradiated lung at 9 and 12 months after radiotherapy. Patient 7 showed slight chest x-ray changes at 6, 9 and 12 months and patient 8 also showed similar changes at 3 and 6 months after radiotherapy in the upper zone of the right irradiated lung. These findings were in keeping with other reports (Hagen et al, 1971; Gross, 1977). The chest x-ray changes occurred in the region which received the irradiation. The radiological changes could be either pulmonary or pleuro-pulmonary. Furthermore, these changes were very slight and started in some patients

at 3 months, and at 6 or 9 months after radiotherapy in others. These radiological changes either cleared and returned to normal, or persisted at the 12 months study. In general, these radiological changes bore no relationship to the changes in lung volumes or T_{CO} changes in 8/10 patients. For example, patients 1, 2, 3 and 9, who had a reduced TLC and RV after radiotherapy, showed no radiological changes, and in patient 10 T_{CO} was reduced at 3 months, but returned back to normal thereafter, whereas her chest x-ray only showed changes at 9 and 12 months after radiotherapy. Moreover, patients 4, 5 and 7 showed chest x-ray changes after radiotherapy without any changes in T_{CO}. Thus it was only two patients (6 and 8) who showed a reduction in T_{CO} which coincided with the changes in their chest x-rays after radiotherapy.

3. Electrocardiographic changes

The electrocardiogram (ECG) was normal and unchanged in the four patients who had radiotherapy on the right side. However, all those six patients who had their radiation to the left side showed ECG changes after radiotherapy, as compared to the control ECG. These ECG changes consisted of flattening or inversion in the T waves in the anterior chest leads after radiotherapy (Figure 49 in patient 6), as noted by Catteral and Ogilvie (1959), Catteral (1960) and Takaoka et al (1968). These T wave changes in the anterior chest leads developed as early as one month after therapy in some patients (4 and 6) or as late as 6 months in others (patient 5). These ECG

changes returned back to normal in one patient (5) at the time of the 12 months study, but the changes persisted in the others.

4. Regional lung function : Lung volume and perfusion

The regional lung function studies showed no significant difference in the regional lung volume (expressed as a % of the total lung capacity, $\frac{E}{E_{Tot}} \times 100 = V\%$ where E = equilibration regional count rate) between the upper 3 segments of the irradiated lung, as compared to the same 3 segments of the non-irradiated lung, either before radiotherapy or at the different intervals after radiotherapy. These findings are in contradiction to those of Prato et al (1977) who found that the regional lung capacity (TLCr) of the irradiated lung apex was reduced at 60 or more days following radiotherapy with Co^{60} in their breast cancer patients. However, their values were calculated as the ratios of the values in the irradiated side to that of the non-irradiated lung apex, and also as the ratio of the average of the measurements at 60 days or more after radiotherapy, as compared to the pre-irradiation values. We suggest that it is intrinsically unlikely that these ratio values were distributed in a Gaussian fashion, but as they do not give individual values, we cannot prove this point. Furthermore, in their technique for measuring the regional lung function, their patients lay supine, unlike the present studies, where the patients were seated, with the lungs vertical. However, these authors reported that the reduction in TLCr

was only minor, and they felt that the reduction in blood flow was responsible for limiting the capacity for function in the irradiated region. In this present study there was a slight reduction at 1 month after radiotherapy in the regional lung volume in the irradiated lung apex, as compared to the non-irradiated apex in 5/7 patients, but in the other two patients there was slight increase in regional volume of the irradiated apex. These changes were slight, and lay within the error expected from simple repetition and could be due to the relative reproducibility of the measurements. The perfusion/alveolus ($\dot{Q}/E\%$), calculated as the average of the upper 3 segments of the irradiated lung, was not significantly different from the average of the upper 3 segments of the non-irradiated lung in the control study. This implies that simple mastectomy had no effect on regional blood flow to these areas. However, at 1 and 6 months the $\dot{Q}/E\%$ was reduced in the irradiated upper lung, as compared to that in the same upper zone of the non-irradiated lung, and this reduction was significant ($P < 0.05$ value) when compared to the control values. However, at 3, 9 and 12 months the reduction in the average $\dot{Q}/E\%$ of the irradiated lung did not reach significance level ($P < 0.20$) when compared to the control values. Although the sequential $\dot{Q}/E\%$ measurements in each patient behaved differently, in general almost all the 7 patients included in calculating the mean values, (as mentioned in the tables and shown in the figures) showed a reduction in $\dot{Q}/E\%$ in the irradiated upper region of the lung

as compared to a similar region in the non-irradiated lung, at different times after radiotherapy, and as compared to the control values. These findings were in keeping with the results of Abe (1974) who reported reduction in pulmonary blood flow after post-operative irradiation for breast cancer patients, as assessed by I^{131} MAA scanning. Furthermore, the results in this present study are in agreement with the findings of Prato et al (1977) who studied their patients before and after five field Co^{60} radiotherapy for breast cancer. These authors found that the ratio of the amount of blood flow to ventilated alveoli [$(\dot{Q})r$] of the irradiated/non-irradiated lung apex after radiotherapy, after being "normalized" to the pre-irradiation value, by dividing the values by the [$(\dot{Q})r$] ratio of the upper zones in the same lungs in the pre-irradiation measurements, was more markedly reduced at about 60 days after therapy than later on. Our results are also in keeping with those of Bake et al (1969) who did <u>not</u> have pre-irradiation "control" measurements, but nonetheless reported reduction in perfusion/unit lung volume (as measured by Xe^{133}) in the <u>lower</u> half of the irradiated lung, as compared with that of the non-irradiated lung, at 2-4 months after radiotherapy, but this reduction was not significant 1-4 months later. Their irradiation technique for breast cancer <u>differs</u> from that used in the present study, since they used conventional radiation therapy with 165-190 KeV, and the treatment was given directly to 3 fields [supra-clavicular, internal mammary (this accounting for the

effects on the lower region) and operative area] with a surface dose of 3000 rads. In addition a fourth field was given tangentially to the lower part of the operative area with a surface dose of 2700 rads. Furthermore, the reduction in perfusion that we have found in this study is in agreement with those reported by Johnson et al (1968) and Goldman et al (1969) who reported the development of ischaemic changes in the irradiated region as detected by lung scans using I^{131} MAA, following irradiation of the lung for intra-thoracic neoplasms. These findings were in agreement with those of Teates (1968), Johnson et al (1970), Korswower et al (1971) and Freedman et al (1974) who showed that thoracic irradiation caused reduction in perfusion of the pulmonary artery of the irradiated lung, as compared to the non-irradiated control lung, in dogs, mice and rabbits respectively, again when studied by lung scans using I^{131} MAA. The histopathological changes in these animal studies following thoracic irradiation showed variable thickening of the alveolar wall with prominence of bizarre enlarged alveolar lining cells, and also marked thickening of media and intimal lining of vessel walls. Pleural thickening was also reported (Teates, 1968).

The reduction in perfusion which we have found could be due to these histopathological changes in the capillaries after irradiation (Gross, 1977). The reduced perfusion/alveolus in the irradiated side at 1, 3 and 6 months, which occurred in all of these 7 patients, could be due to changes in the endothelial cells, leading to swollen and obstructed capillaries in the irradiated area

(Phillips, 1966; Phillips et al, 1972). Later at 9 and 12 months the slowly dividing capillary endothelial cells may have responded to a feedback stimulus to divide rapidly (Ellis, 1967) so that regenerated new capillaries are found which improved the perfusion in the irradiated area. Furthermore, some of this improvement may be due to a physiological reduction in the local vascular resistance by opening up new channels (recruitment) and by distension of those already open (Hughes, 1976). This improvement in perfusion occurred as early as 3 months in some patients (3 and 6), and as late as 12 months in others (patient 1). The reason for the perfusion/alveolus not returning back to the pre-irradiation value in the irradiated lung in most of these patients is presumed to result from a loss of capillaries caused by irradiation (Gross, 1977).

The reduction in perfusion/alveolus in the irradiated region is most probably a genuine reaction to the radiation dosage, since it happened only in the irradiated lung, and only in the region corresponding to that irradiated, and did not develop in the corresponding regions of the non-irradiated lung. Moreover, these changes occur sequentially following radiotherapy and coincide with the pathological changes observed in experimental animals after irradiation (Gross, 1977). Furthermore, they could not have arisen from an increase in lung volume in the irradiated area (as the $\dot{Q}$ values of each segment are divided by E values for that segment to give the $\dot{Q}/E$ values), as there was no significant change

in the regional lung volume (V%) after radiotherapy, as compared to control, where $V\% = \frac{E}{E_{Tot}} \times 100$, as mentioned earlier. Moreover, values for the reciprocal (1/E) in the upper 3 segments of the irradiated lung and those of the non-irradiated lung were calculated before and at the different intervals after radiotherapy, and again found to be not changed. As the relation between E and 1/E is a rectangular hyperbola, a small undetected change in E might cause larger change in 1/E, and thus will affect the values of $\dot{Q}/E$, in turn. However, this was not the case, as calculated values of 1/E were unchanged.

Regional ventilation

The average value of ventilation/alveolus ($\dot{V}/E\%$) at an inspiratory flow rate of 0.2 L/sec in the upper 3 segments of the irradiated lung was not significantly different from the average of the non-irradiated lung in the control study. The results in this measurement showed wide scatter, with a different response in each patient, which probably resulted from the difficulty in voluntarily controlling this low constant inspiratory flow rate up to total lung capacity. In general, no significant change could be detected in the mean values for the 7 patients at different intervals after radiotherapy, as compared to the control value. Six out of 7 of these patients showed some reduction in ventilation at 1 month and/or 3 months, which increased thereafter, in keeping with the findings of Prato et al (1977) [although the inspiratory flow rate was not mentioned in their study]. This reduction could be

due to the formation of some fibrin, haemorrhages and debris in the alveolar space, in addition to the oedema, debris, infiltrated inflammatory cells and increased connective tissue in the interstitial spaces, as a result of irradiation (Gross, 1977). The reduction in ventilation/alveolus in the irradiated lung after radiotherapy is neither due to an increase in regional lung volume (V%) nor due to a decrease in 1/E, as mentioned earlier. Therefore, this reduction in ventilation/alveolus of the irradiated upper lung could be due to a reduction in the compliance of the upper zone of the irradiated lung, as the distribution of ventilation at such a low inspiratory flow rate is determined mainly by the regional compliance (Dollfuss et al, 1966; Bake et al, 1974). To confirm this suggestion, the ratio of $\dot{V}/E\%$ at 0.2 L/sec $\dot{V}/E$ (0.2) of the upper 3 segments to that of $\dot{V}/E$ (0.2) of the lower 3 segments of the same lung was calculated for each side, in each patient before and at different intervals after radiotherapy. The ratio of this compliance of the upper to that of the lower zones of the same lung (C_U/C_L) can be assessed by the distribution of ventilation of a Xe^{133} bolus inspired at this low flow rate (0.2 L/sec) (Bake et al, 1974). This concept depends on the theoretical response of two-compartment lung model having different regional time constants (Pedley, Sudlow and Milic-Emili, 1972). Figure 60 shows the two-compartment model of the lung as applied in this study, where C_U, R_U and $\dot{V}_U$ are the compliance, resistance and the flow of the upper zone respectively, and C_L, R_L and $\dot{V}_L$ are the compliance,

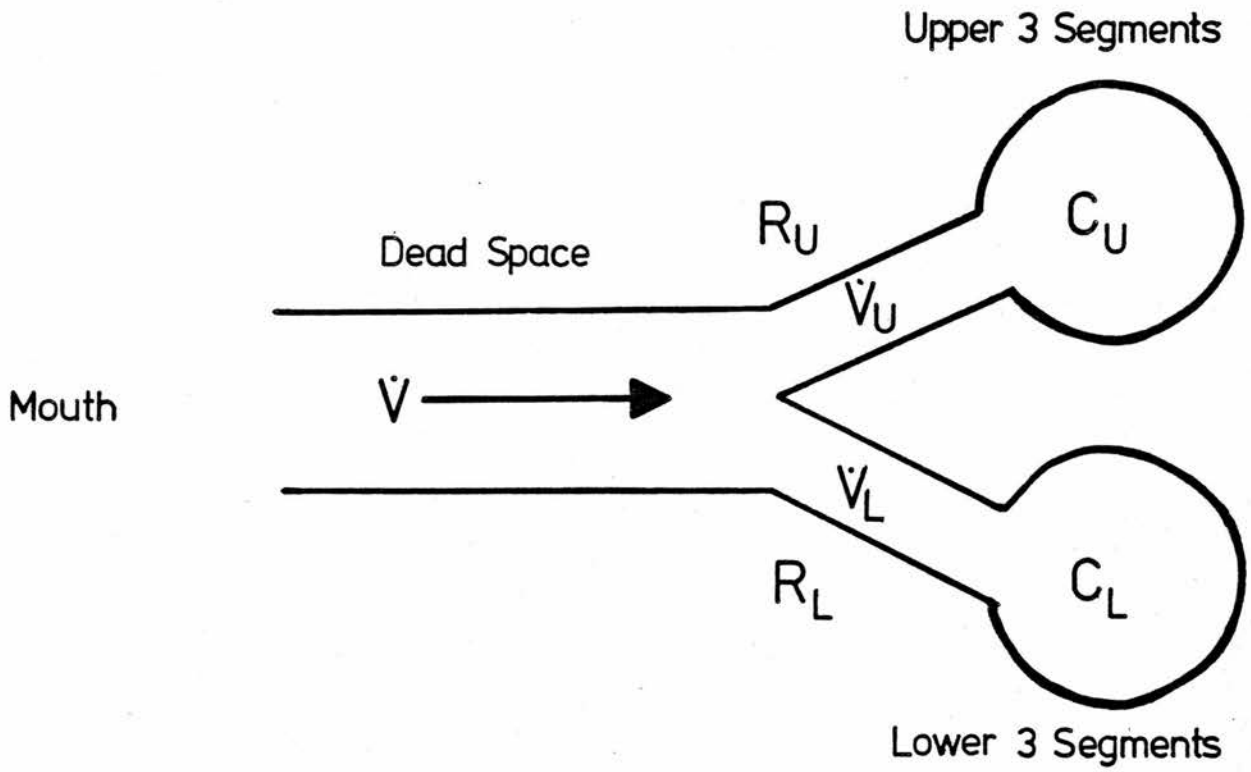


Figure 60

A schematic diagram of the two-compartment model of the lung (After Pedley et al, 1972).

C_U, C_L = the compliances of the upper and lower 3 segments respectively

R_U, R_L = the resistances of the upper and lower 3 segments respectively

$\dot{V}_U, \dot{V}_L$ = the flows of the upper and lower 3 segments respectively

resistance and the flow of the lower zone respectively. The dead space is the volume of the apparatus and of the airways down to the bifurcation and including the main bronchi. At very small flow rates, when the mechanics of the lung are dominated by elastic effects, equation (30) of Pedely et al (1972) is applicable, i.e.:

$$\Delta P_{EU} = \Delta P_{EL} + \Delta P_G \quad \text{----- (1)}$$

Where ΔP_{EU} is the elastic pressure drop between the point of bifurcation and the upper zone

ΔP_{EL} is the elastic pressure drop between the point of bifurcation and the lower zone

ΔP_G is the difference in pleural pressure between the centres of mass of the upper and lower zones as a result of the vertical gradient in pleural pressure (Dollfuss et al, 1967; Hughes et al, 1970)

In the linear P-V relationship model of Pedely et al, this equation is written as:

$$\frac{V_U}{C_U} = \frac{V_L}{C_L} + \Delta P_G \quad \text{----- (2)}$$

Since $P_{EU} = V_U/C_U$

and $P_{EL} = \frac{V_L}{C_L}$

Where C_U and C_L are constant compliances of the two zones and V_U and V_L are the volume of the two zones

Upon differentiating this equation ----- (2) with respect to time, these authors obtained the following equation:

$$\dot{V}_U/C_U = \dot{V}_L/C_L$$

i.e. $$\frac{\dot{V}_U}{\dot{V}_L} = \frac{C_U}{C_L}$$

Therefore, the ventilation ratio (0.2 L/sec) of the upper 3 segments to the lower 3 segments ($\dot{V}_U/\dot{V}_L$) of irradiated and non-irradiated lung was calculated in each patient, so as to measure the compliance ratio (C_U/C_L) of each lung before and after radiotherapy. For example, in patient 1, the values of $\dot{V}_U/\dot{V}_L$ and thus of C_U/C_L for each lung in the pre-radiotherapy "control" study and at different times after radiotherapy are:

Patient 1 Values of compliance (upper zone)/compliance (lower zone) = $C_U/C_L = \dot{V}_U/\dot{V}_L$

Control		1 month		3 months		6 months		9 months		12 months	
Irr	Non-Irr	Irr	Non-Irr	Irr	Non-Irr	Irr	Non-Irr	Irr	Non-Irr	Irr	Non-Irr
0.98	0.93	0.73	1.26	0.46	0.79	0.68	0.85	0.47	0.69	0.73	0.72

These ratios of $\dot{V}_U/\dot{V}_L$ and thus C_U/C_L were not different between the two sides in the control study. However, at 1, 3, 6 and 9 months after radiotherapy the C_U/C_L of the irradiated side was markedly reduced (possibly due to reduction in the compliance of the upper zone), when compared to the values of the non-irradiated side. On the other hand, the C_U/C_L ratio at 12 months study was almost the same in both sides, but the values of the ratio were less than those before irradiation. Moreover, the dead space volume, which determines the time taken for the Xe^{133} bolus to be vertically distributed was unchanged throughout the study (i.e. the volume of the apparatus and of the airways

between the point where the Xe^{133} bolus given at the mouth down to the bifurcation and including the main bronchi as shown in Figure 60. Thus these findings support the suggestion that the compliance of the irradiated lung was reduced. This is in agreement with the findings of Sweany et al (1959) and Teates (1965) after thoracic irradiation in experimental animals (dogs). The pathology of the irradiated lungs in these animals confirmed the radiation damage in these lungs. Such a reduction in compliance of the irradiated lungs was also observed in rats following experimental irradiation (Naimark et al, 1970; Shrivastava et al, 1974).

The ventilation/alveolus ($\dot{V}/E\%$) at the higher inspiratory flow rate of 1.5 L/sec, again expressed as the average value of the upper 3 segments of each lung, was slightly lower in the irradiated lung than the non-irradiated lung in the pre-irradiation "control" study, but this difference was not significant. At 1 and 3 months after therapy the ventilation/alveolus increased in the upper zone of the irradiated lung, but was still not different from that in the non-irradiated lung, nor from the values in the control study. However, at 6 months all the patients showed greater ventilation/alveolus at 1.5 L/sec in the upper zone of the irradiated lung, as compared to those of the non-irradiated lung and this difference was significantly greater ($P < 0.05$) than the difference between the two sides in the control study. Later, at 9 and 12 months, the ventilation/alveolus was reduced, so that there were then

no significant differences, either between the two lungs, or when compared to the control values. The increase in ventilation/alveolus in the irradiated lung at 6 months after radiotherapy could not be attributed to a decrease in regional lung volume (V%), nor to an increase in 1/E (as mentioned earlier). It seems unlikely that this increase in ventilation in the irradiated lung at 6 months was caused by practice in the respiratory manoeuvre, because it was not shown in the 9 and 12 month studies. Another possibility to account for this increase in ventilation could be a reduction in the regional airway resistance in the irradiated lung zones, because at this high inspiratory flow rate the distribution of regional ventilation is mainly determined by the regional resistance (Robertson et al, 1969; Bake et al, 1974). This reduction in regional airway resistance may arise from dynamic distension of the intra pulmonary airways, caused by reduction in the applied regional pleural pressure (Bake et al, 1974; Pedely et al, 1972), which in turn could be due to the reduction in the compliance of the irradiated region and a local increase in the elastic recoil pressure, the pathophysiological basis for this compliance change being discussed previously.

5. Summary

In summary, the results of this sequential study showed that this dose and technique of radiotherapy caused:

A. Reduction in TLC and RV (i.e. restrictive type of ventilation defect), which could be due to:

1. Diminution in regional volume of the irradiated zone caused by the encroachment of the interstitial tissue into the alveolar spaces, some of which become replaced later by fibrous tissue.

2. Local distortion of the intrapleural pressure over the irradiated region, due to the local reduction in compliance, as shown by the distribution of the regional ventilation during slow inspiration.

3. Thickening of the pleura, locally in the irradiated zone, may contribute to this reduction in local distension of the lung in this zone.

B. Defective gas transfer in 3 out of 10 patients which was presumably due to reduction in local area or increase in local thickness of the diffusing membrane (Dm).

C. Marked reduction in regional perfusion to each alveolus in the irradiated upper zones of the lung, which may be caused by destruction and obstruction of the regional capillary bed.

D. Slight reduction in the regional ventilation/alveolus at a low inspiratory flow rate in 6 out of 7 patients, as a result of the transient diminution in the regional compliance in the irradiated area, which may be due to diffuse pulmonary reaction in the irradiated lung parenchyma.

E. Increased regional ventilation/alveolus at a high inspiratory flow rate, due to reduction in regional airway resistance, caused by dynamic distension of intrapulmonary airways in the irradiated region.

F. No regional lung volume reduction could be detected in these patients which may be due to redistribution in lung volume from zones with high lung volume to other zones with low lung volume, as the upper 3 segments are studied by the gamma camera field throughout, and if this region of the lung became smaller and fibrosed, the lower segment (i.e. segment 4) might be pulled and thus occupy part of the upper 3 segment field originally studied.

ii) Cross-sectional Study

This study identified two groups of patients, both of whom had simple mastectomy followed by radiotherapy for their breast cancer, one group showing radiological changes attributed to the radiotherapy, whereas the other group did not show such radiological changes. However, there was no significant difference between these two groups with respect to their mean values of age, height, weight, nor in their smoking history, or mean values of overall lung function (TLC, VC, RV, RV/TLC%, FEV_1, FVC, FEV_1/FVC%, $\dot{V}_{max}$ 50, $\dot{V}_{max}$ 30, T_{CO} and sGaw) or the mean values of regional lung function measurements (V%, $\dot{Q}$/E% and $\dot{V}$/E%).

Both groups showed normal TLC values for all these patients, when expressed as the mean value, and also as a percentage of the prediced normal value, when studied between 1-14 years after radiotherapy. The TLC values in these patients were either unchanged after radiotherapy, or alternatively the unknown control values before treatment were higher than 100% of the predicted value, and subsequently fell. However, this cross-sectional study provides no

evidence that the TLC changed systematically after radiotherapy in these patients, as pre-irradiation "control" values in each individual are not available. The findings of the sequential studies and those of previous work (Emirgil and Heinemann, 1961) nonetheless make it possible that their TLC had fallen after radiotherapy. Furthermore, 36/48 of patients in this study had RV values below 100% of the predicted normal value, which supports the possibility that RV was reduced following radiotherapy. However, 12/48 of these patients from both groups had an RV value of over 100% predicted, but as all of these 12 patients were smokers, this might explain this finding (Woolf and Suero, 1971).

Moreover, the FEV_1 in the 37/48 of these patients showed values over 100% predicted, which may also be due to the effect of radiotherapy in causing a regional increase in the elastic recoil of the lung, and thus increased the calibre of the airway relative to the size of the lung (as discussed before). However, in those 11/48 patients in whom the FEV_1 was reduced, again all were smokers which might explain this finding (Woolf and Suero, 1971).

Furthermore, T_{CO} values in all but 4 patients (both smokers and non-smokers) were low, being on average about 76% of the predicted normal values in both groups, which was probably due to the effect of radiotherapy in causing a reduction in area, or increase in thickness of the diffusing membrane (Dm), in addition to the effect of smoking (Woolf and Suero, 1971). However, this cross-sectional study does not provide firm evidence to attribute the low values

of T_{CO} to the effect of radiotherapy, as again the pre-radiotherapy "control" measurements are not available.

The results of this cross-sectional study do indicate that the radiological findings attributed to the radiotherapy bore no relation to the low values of T_{CO} or to the high values of FEV_1 in these patients, which supports the findings in the smaller number of patients followed in the sequential longitudinal study. The ECG changes attributed to radiotherapy were present in 11/19 of these patients who had their radiotherapy on the left side, and these ECG changes bore no relationship to the time following radiotherapy. Again, we cannot be certain that these changes were due to a radiation effect, but the changes were similar to those found in the sequential study, and in previous work (Catteral et al, 1959; Takaoka et al, 1968) and it seems probable that they arose as a result of the radiotherapy.

The regional lung function measurements in this study showed similar results to those found in the sequential study, in that the regional perfusion/alveolus ($\dot{Q}/E\%$), which was assessed by Tc^{99m} MAA, was reduced in the upper region of the irradiated lung, as compared to that of the non-irradiated lung, whereas there was no difference in either in the regional lung volume (V%) or in the regional distribution of ventilation/alveolus ($\dot{V}/E\%$ at 0.5 L/sec) between the upper regions of the irradiated lung and those of the non-irradiated lung.

The reduction in perfusion/alveolus ($\dot{Q}/E\%$) in the irradiated side was present in 40/48 of these patients and

was presumably due to destruction and obstruction of the pulmonary capillary bed in the irradiated region (Gross, 1977). The magnitude of the reduction in perfusion/alveolus was not related to the side of radiotherapy, the time in years after radiotherapy or to the severity of the radiological changes attributed to the radiotherapy.

The regional ventilation/alveolus in this study was measured at an inspiratory flow rate of 0.5 L/sec. The ventilation/alveolus in the upper region of both lungs was not different, which is in contradiction to the findings of Prato et al (1977). This could again be because they calculated their statistical significance from the ratios between the irradiated and the non-irradiated lung regions; whereas in this present study the results were calculated as differences, as differences tend to be distributed in a Gaussian manner, whereas ratios are not. Furthermore, Prato et al (1977) reported reduction in the volume of the irradiated region, as compared to the non-irradiated region, and this reduction in regional volume could account for the reduction in ventilation in their data. The truth of this assumption is supported by the fact that the reductions in both the regional volume and in the regional ventilation/alveolus are the same, 0.78 and 0.79 respectively.

In the present study we could not detect any changes in regional lung volume in the irradiated lung of these patients, as compared to the non-irradiated lung, again in contrast to the findings of Prato et al (1977). However, this could be due to the redistribution of lung volume, some

normal alveoli possibly displacing the damaged fibrosed alveoli in this long term study. Prato et al (1977) calculated their results on the ratios between the two sides, which might be thought to magnify the picture more than expressing the results as differences; for example, the difference between 0.8 and 1.0 is only 0.2, whereas a ratio of 0.8/1.0 is 80%.

iii) Summary

The primary aim was to study the effects of the Edinburgh routine radiotherapy given for breast cancer on the total and regional lung function in women with normal lungs. This study has succeeded in identifying that this treatment caused a slight restrictive defect in overall pulmonary function, but mainly a reduction in the regional perfusion/alveolus in the irradiated lung zones. Thus the earliest and main effect of radiotherapy is upon the pulmonary vascular bed in the irradiated region. This effect seems likely to have happened in most of these patients, and was found to be present from as little as 1 month after radiotherapy (sequential study) to as long as 14 years after radiotherapy (cross-sectional study).

We did not have the opportunity in this study to include sufficient patients in the sequential study to predict those who would subsequently develop symptomatic radiation pneumonitis in its severe form and which ones would not. A firm answer to this question will require the sequential study of a larger series of patients, but it

does seem that the methods utilised in the present study, particularly the measurements of regional performance and estimates of regional compliance, will prove to be sufficiently sensitive for this purpose.

V. CONCLUSIONS

It was concluded from this study that:

1. A radiation dose of 4250 rads "to max", delivered in 10 fractions over 4 weeks to the axilla and supraclavicular region in the treatment of breast cancer, had little effect on overall lung function in these 10 women who had normal chest x-rays and pulmonary function before radiotherapy.

2. However, perfusion to the alveoli in the irradiated region was reduced, without clinical or radiological changes, from as little as one month, to as long as 14 years after radiotherapy, in 27 patients.

3. The earliest effect of radiotherapy appears to be upon the pulmonary vascular bed of the irradiated region.

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CLINICAL AND FUNCTIONAL MEASUREMENTS IN 10 WOMEN BEFORE RADIOTHERAPY BUT AFTER SIMPLE MASTECTOMY
(Control Measurements)

Smoking	Height metres	Weight Kgs	Histopathological Diagnosis of Tumour	Stage	Side	Hb gm/dl	WBC x10^9/L	ECG	Chest x-ray	TLC litres	VC litres	RV litres	RV/TLC %	FEV_1 litres	FVC litres	FEV_1/FVC %	$\dot{V}_{max}$ 50 L/sec	$\dot{V}_{max}$ 30 L/sec	TC_O mmol/min/kPa	sGaw sec^{-1}kPa^{-1}	Regional Lung Function: Upper 3 (treated) - Upper 3 (non-treated) V. %	$\dot{Q}/E$ %	$\dot{V}/E$ % @ 0.2 L/s	$\dot{V}/E$ % @ 1.5 L/s
NS	1.66	58.0	Poorly differentiated	II	R	13.6	5.5	N	N	6.61 (128.6%)	3.69 (117.9%)	2.92 (161.3%)	44 (129.4%)	2.95 (126.6%)	3.50 (123.2%)	84 (105.0%)	ND	ND	6.70 (75.9%)	ND	0.47	0.65	-10.80	9.71
S	1.57	49.0	Highly sclerosing	I	R	15.3	5.8	N	N	5.05 (119.1%)	2.60 (106.6%)	2.44 (147.0%)	48 (129.7%)	1.80 (98.9%)	2.05 (92.8%)	88 (115.8%)	ND	ND	4.08 (51.3%)	ND	1.13	-15.57	-5.44	-0.10
NS	1.70	64.0	Anaplastic	II	L	13.7	5.0	N	N	5.77 (113.4%)	2.83 (94.3%)	2.95 (154.5%)	51 (145.7%)	2.60 (118.7%)	3.25 (85.8%)	80 (102.6%)	3.55	2.32	6.45 (73.6%)	1.392	-0.13	-0.13	-5.90	3.21
NS	1.67	65.5	Anaplastic	I	L	12.2	5.3	1°HB	N	5.70 (108.4%)	4.51 (139.6%)	1.20 (66.3%)	21 (63.6%)	3.55 (147.3%)	4.05 (138.2%)	88 (110.0%)	3.96	1.48	5.59 (62.5%)	1.228	0.14	-10.03	-7.11	-12.80
NS	1.65	66.0	Adeno Ca.	II	L	14.3	5.4	N	N	5.01 (103.7%)	2.98 (107.6%)	2.03 (106.3%)	41 (109.9%)	2.10 (102.9%)	2.55 (98.0%)	84 (109.5%)	2.40	1.20	6.27 (73.4%)	1.139	-0.4*	-8.20*	-53.90*	-35.60*
NS	1.70	78.3	Mucoid Ca.	I	L	12.6	4.3	N	N	6.81 (126.4%)	4.25 (131.6%)	2.56 (130.6%)	38 (111.1%)	3.25 (136.6%)	4.05 (137.3%)	80.3 (100.4%)	4.54	1.90	7.86 (86.7%)	1.327	-0.73	-5.10	25.32	-9.64
XS	1.70	83.7	Invasive Ca.	II	R	13.8	7.0	N	N	5.72 (109.4%)	2.26 (74.8%)	3.46 (168.8%)	61 (165.8%)	1.50 (70.8%)	1.70 (63.7%)	88 (110.0%)	1.68	0.95	5.77 (63.6%)	0.676	0.80	-34.88	-22.80	10.11
NS	1.70	60.0	Scirrhous Ca.	II	R	12.4	5.2	N	N	5.84 (109.4%)	4.05 (127.8%)	1.79 (164.2%)	31 (88.6%)	2.95 (126.6%)	4.00 (137.5%)	74 (93.7%)	3.08	1.38	9.08 (100.6%)	0.920	-0.77	-5.60	-0.20	-12.51
NS	1.74	92.7	Scirrhous Ca.	I	L	10.8	4.4	N	N	5.47 (95.0%)	3.88 (110.5%)	1.59 (77.6%)	29 (88.4%)	3.05 (117.8%)	3.10 (95.7%)	98.4 (118.7%)	4.16	2.50	6.71 (91.5%)	1.478	-0.27	14.10	-0.13	-19.93
NS	1.59	49.0	Intraduct Ca.	I	L	13.2	6.4	N	N	5.02 (105.2%)	3.78 (125.2%)	1.24 (82.1%)	25 (80.6%)	3.40 (143.5%)	3.80 (136.2%)	89.5 (107.8%)	5.15	2.94	7.48 (88.1%)	1.640	-0.06	1.90	2.80	-7.00
-	1.67 ±0.02	66.6 ±4.5								5.70 (111.9%) ±0.2	3.48 (113.6%) ±0.2	2.22 (125.9%) ±0.2	39 (111.3%) ±4.0	2.72 (119.0%) ±0.2	3.21 (110.8%) ±0.3	85 (107.4%) ±2.1	3.57 ±0.4	1.83 ±0.25	6.60 (76.7%) ±0.4	1.240 ±0.11	-0.19 ±0.2	-0.60 ±2.9	0.06 ±4.5	-7.00 ±3.8

*Results possibly incorrect because of malpositioning of patient.

TABLE 2A

Patient 1

Non-smoker, 44 years. Stage II Anaplastic Carcinoma of Right Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4035 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	6.61 (128.6%)	6.19 (120.4%)	5.63 (109.5%)	5.27 (102.5%)	5.15 (100.2%)	5.40 (105.0%)
VC (litres)	3.69 (117.9%)	4.00 (127.8%)	3.84 (122.7%)	3.30 (105.4%)	3.45 (110.2%)	3.35 (107.0%)
RV (litres)	2.92 (161.3%)	2.19 (121.0%)	1.79 (98.9%)	1.97 (108.8%)	2.06 (113.8%)	2.05 (113.3%)
RV/TLC (%)	44% (129.4%)	35% (102.9%)	32% (94.1%)	37% (108.8%)	37% (108.8%)	38% (111.8%)
FEV_1 (litres)	2.95 (126.6%)	2.95 (126.6%)	3.05 (130.9%)	3.05 (130.9%)	2.85 (122.3%)	3.00 (128.8%)
FVC (litres)	3.50 (123.2%)	3.60 (126.8%)	3.65 (128.5%)	3.55 (125.0%)	3.50 (123.2%)	3.35 (118.0%)
FEV_1/FVC (%)	84% (105.0%)	82% (102.5%)	84% (105.0%)	86% (107.5%)	81.4% (101.8%)	90% (112.5%)
$\dot{V}_{max}$ 50 (L/sec)	ND	ND	ND	ND	ND	ND
$\dot{V}_{max}$ 30 (L/sec)	ND	ND	ND	ND	ND	ND
TC_O (mmol/min/kPa)	6.70 (75.9%)	6.17 (69.9%)	6.38 (72.3%)	7.52 (85.2%)	6.66 (75.4%)	8.09 (91.6%)
sGaw ($sec.^{-1}kPa^{-1}$)	ND	1.009	0.911	1.287	1.789	1.486
ECG	Normal	Normal	Normal	Normal	Normal	Normal
Chest x-ray	Normal	Normal	Normal	Normal	Normal	Normal

ND = Not done % Predicted values given in brackets

TABLE 2B

Patient 1

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top 1	60.0	51.0	9.0	32.8	65.9	-33.1	37.0	76.0	-39.0	30.0	110.0	-80.0	34.0	67.0	-33.0	41.0	51.0	-10.0
2	58.5	71.0	-12.5	45.5	75.1	-29.5	37.0	60.0	-23.0	37.0	66.0	-29.0	34.0	76.0	-42.0	57.0	68.0	-11.0
3	87.0	82.0	5.0	58.0	82.6	-24.6	54.0	78.0	-24.0	64.0	75.0	-11.0	45.0	74.0	-29.0	73.0	89.0	-16.0
4	91.0	98.0	-7.0	88.4	102.6	-14.2	84.0	106.0	-22.0	79.0	98.0	-19.0	70.0	93.0	-23.0	99.0	107.0	-8.0
5	110.0	100.0	10.0	109.5	127.0	-17.5	100.0	122.0	-22.0	104.0	116.0	-12.0	88.0	112.0	-24.0	111.0	122.0	-11.0
6	121.0	129.0	-8.0	133.6	125.7	7.9	124.0	143.0	-19.0	126.0	127.0	-1.0	111.0	136.0	-25.0	119.0	130.0	-11.0
7	123.0	136.0	-13.0	129.0	145.8	-15.9	140.0	141.0	-1.0	138.0	151.0	-13.0	127.0	155.0	-28.0	123.0	141.0	-18.0
Bottom 8	147.0	131.0	16.0	129.2	151.1	-21.9	126.0	127.0	-1.0	161.0	163.0	-2.0	150.0	174.0	-24.0	114.0	123.0	-9.0

TABLE 2C

Patient 1

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

	Lung Volume %	Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	5.23	5.64	-0.4	5.30	3.80	1.5	2.30	1.40	0.9	4.40	3.70	0.7	2.70	2.20	0.5	3.30	4.30	-1.0
	2	6.42	4.70	1.7	6.60	5.40	1.2	5.70	4.90	0.8	6.50	5.30	1.2	5.40	4.80	0.6	6.30	6.40	-0.1
	3	6.40	6.30	0.1	8.20	6.10	2.1	8.10	7.30	0.8	7.50	6.70	0.8	6.60	5.80	0.8	7.60	6.90	0.7
	4	8.00	6.50	1.5	7.60	7.10	0.5	8.70	8.10	0.6	8.50	7.70	0.8	8.40	7.20	1.2	8.40	7.50	0.9
	5	7.50	6.40	1.1	7.50	7.00	0.5	10.0	8.20	1.8	8.20	8.10	0.1	8.90	7.80	1.1	8.10	7.40	0.7
	6	8.00	5.90	2.1	7.20	6.80	0.4	8.80	7.20	1.6	7.30	7.60	-0.3	8.70	7.10	1.6	7.80	7.10	0.7
	7	7.50	5.60	1.9	6.60	6.00	0.6	6.30	6.20	0.1	5.60	6.20	-0.2	7.30	6.70	0.6	6.00	6.00	0.0
Bottom	8	4.60	4.10	0.5	4.90	4.10	0.8	3.50	3.30	0.2	3.20	3.40	-0.2	4.90	5.40	-0.5	3.80	3.30	0.5

TABLE 2D

Patient 1

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	80.0	97.0	-17.0	59.1	107.3	-48.2	34.0	44.0	-10.0	63.0	55.0	8.0	43.0	39.0	4.0	79.0	52.0	27.0
	2	102.0	117.0	-15.0	77.7	142.0	-64.3	65.0	66.0	-1.0	88.0	75.0	13.0	67.0	54.0	13.0	93.0	67.0	26.0
	3	100.0	105.0	-5.0	86.3	93.8	-7.5	81.0	84.0	-3.0	108.0	81.0	27.0	86.0	76.0	10.0	106.0	82.0	24.0
	4	89.5	103.0	-13.5	112.4	96.5	15.9	99.0	103.0	-4.0	114.0	98.0	16.0	107.0	82.0	25.0	114.0	87.0	27.0
	5	93.0	96.0	-3.0	126.1	105.9	20.2	115.0	94.0	21.0	128.0	98.0	30.0	118.0	95.0	23.0	120.0	90.0	30.0
	6	85.0	101.0	-16.0	141.9	91.3	50.6	142.0	90.0	52.0	129.0	86.0	43.0	133.0	92.0	41.0	127.0	96.0	31.0
	7	98.0	125.0	-27.0	141.2	90.1	51.1	157.0	95.0	62.0	135.0	83.0	52.0	147.0	86.0	61.0	137.0	100.0	37.0
Bottom	8	117.0	118.0	-1.0	127.3	89.3	38.0	149.0	97.0	52.0	140.0	91.0	49.0	189.0	91.0	98.0	134.0	90.0	44.0

TABLE 2E

Patient 1

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

V/E % (1.5 L/s)	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top 1	106.0	74.0	32.0	68.4	56.9	11.5	49.0	66.0	-17.0	78.0	80.0	-2.0	69.0	80.0	-11.0	94.0	65.0	29.0
2	96.0	108.0	-12.0	85.8	72.3	13.5	80.0	84.0	-4.0	89.0	94.0	-5.0	83.0	84.0	-1.0	102.0	91.0	11.0
3	108.0	100.0	8.0	88.9	82.1	6.8	95.0	97.0	-2.0	108.0	99.0	9.0	94.0	106.0	-12.0	104.0	110.0	-6.0
4	106.0	86.0	20.0	107.9	99.1	8.8	109.0	118.0	-9.0	105.0	108.0	-3.0	98.0	111.0	-13.0	107.0	108.0	-1.0
5	116.0	81.0	35.0	117.8	118.5	-0.7	108.0	111.0	-3.0	109.0	111.0	-2.0	102.0	108.0	-6.0	107.0	111.0	-4.0
6	100.0	85.0	15.0	124.5	115.6	8.9	119.0	104.0	15.0	111.0	100.0	11.0	112.0	105.0	7.0	100.0	100.0	0.0
7	120.0	86.0	34.0	117.5	105.2	12.3	103.0	89.0	14.0	102.0	88.0	14.0	110.0	92.0	18.0	94.0	99.0	5.0
Bottom 8	144.0	85.0	59.0	102.6	103.1	-0.5	89.0	84.0	5.0	93.0	86.0	7.0	107.0	93.0	14.0	86.0	87.0	-1.0

TABLE 3A

Patient 2

Smoker, 61 years. Stage I Highly Sclerosing Lobular & Infiltrative Carcinoma of Right Breast - Treated by Simple Mastectomy Followed by Radiotherapy (Maximum dose 4250 rads : Minimum central dose 4070 rads)

Overall Lung Function Measurements	Control	1 month		24 months
TLC (litres)	5.05 (119.1%)	5.10 (120.3%)		5.04 (118.9%)
VC (litres)	2.60 (106.6%)	3.10 (127.1%)		2.61 (107.0%)
RV (litres)	2.44 (147.0%)	2.00 (120.5%)		2.43 (146.4%)
RV/TLC (%)	48% (129.7%)	39% (105.4%)		48% (129.7%)
FEV_1 (litres)	1.80 (98.9%)	1.85 (101.7%)		1.80 (100.6%)
FVC (litres)	2.05 (92.8%)	3.00 (135.8%)	Patient declined further study until 24 months	2.60 (118.2%)
FEV1/FVC (%)	88% (115.8%)	62% (81.6%)		69% (91.0%)
$\dot{V}_{max}$ 50 (L/sec)	ND	ND		1.45
$\dot{V}_{max}$ 30 (L/sec)	ND	ND		0.64
TC_0 (mmol/min/kPa)	4.08 (51.3%)	4.55 (57.2%)		4.22 (53.1%)
sGaw ($sec.^{-1}kPa^{-1}$)	0.962	0.889		0.889
ECG	Normal	Normal		Normal
Chest x-ray	Normal	Normal		Normal

ND = Not done % Predicted values given in brackets

TABLE 3B

Patient 2

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %		Control			1 month				24 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff		Irr	Non-Irr	Diff
Top	1	69.9	80.4	-10.5	54.1	60.9	-6.8		47.7	104.0	-56.3
	2	61.3	80.5	-19.2	46.5	66.1	-19.6		55.6	81.0	-25.4
	3	85.1	97.1	-12.0	64.5	84.2	-20.2		73.7	101.6	-27.9
	4	104.7	104.7	0.0	85.3	107.1	-21.8	Patient declined further study until 24 months	96.4	117.7	-21.3
	4	121.1	115.9	5.2	109.0	127.2	-18.2		107.5	122.4	-14.9
	6	116.3	114.1	2.2	116.7	128.6	-11.9		109.1	124.5	-15.4
	7	114.7	100.5	14.2	124.0	134.5	-10.5		108.7	121.5	-12.8
Bottom	8	112.5	90.7	21.8	119.2	139.3	-20.1		79.1	107.3	-28.2

TABLE 3C

Patient 2

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month				24 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff		Irr	Non-Irr	Diff
Top	1	4.44	2.32	2.12	2.10	2.00	0.10		3.6	2.9	0.5
	2	6.76	5.62	1.14	5.10	5.80	-0.70		5.8	5.4	0.4
	3	7.75	7.63	0.12	7.60	8.10	-0.50		7.8	6.6	1.2
	4	8.19	7.78	0.41	8.70	9.60	-0.90	Patient declined further study until 24 months	6.9	6.3	0.6
	5	8.05	7.35	0.70	8.70	9.80	-1.10		9.2	8.3	0.9
	6	7.49	7.23	0.26	7.50	9.20	-1.70		8.4	7.6	0.8
	7	6.67	7.18	-0.51	5.30	6.30	-1.00		6.7	6.4	0.3
Bottom	8	4.43	2.68	1.75	1.90	2.40	-0.50		4.6	3.7	0.9

TABLE 3D

Patient 2

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)		Control			1 month				24 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff		Irr	Non-Irr	Diff
Top	1	97.3	76.1	21.2	86.9	87.0	-0.1		69.0	99.7	-30.7
	2	92.8	96.7	-3.9	93.6	104.0	-10.4		90.9	101.7	-10.8
	3	96.8	111.6	-14.8	98.0	105.9	-7.0		90.7	110.0	-19.3
	4	90.2	111.0	-20.8	91.1	120.8	-29.7	Patient declined further study until 24 months	90.6	117.1	-26.5
	5	96.7	110.7	-14.0	83.7	125.5	-41.8		88.3	124.0	-35.7
	6	94.6	99.6	-5.0	85.4	114.3	-28.9		96.7	111.1	-14.4
	7	96.2	108.2	-12.0	78.6	117.5	-38.9		108.0	109.9	-1.9
Bottom	8	98.9	100.7	-1.8	67.1	109.8	-42.7		77.5	91.2	-13.7

TABLE 3E

Patient 2

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month				24 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff		Irr	Non-Irr	Diff
Top	1	124.7	104.4	20.3	93.4	72.5	20.9		98.0	117.9	-19.9
	2	110.5	105.2	5.3	95.7	85.4	10.0		103.9	104.2	-0.3
	3	105.7	119.4	-13.7	107.8	85.8	22.0		97.8	112.7	-14.9
	4	97.7	113.3	-15.6	101.4	93.2	8.2	Patient declined further study until 24 months	95.8	114.6	-18.8
	5	99.6	104.4	-4.8	104.3	111.2	-6.9		93.2	121.1	-27.9
	6	91.2	91.9	-0.7	100.4	114.7	-14.3		95.6	104.2	-8.6
	7	75.5	84.6	-9.1	98.0	111.9	-13.9		94.4	99.2	-4.8
Bottom	8	84.1	77.7	6.4	75.3	103.3	-28.0		65.0	67.2	-2.2

TABLE 4A

Patient 3

Non-smoker, 54 years. Stage II Anaplastic Carcinoma of Left Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4114 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.77 (113.4%)	5.45 (107.1%)	5.48 (107.7%)	5.16 (101.4%)	4.93 (96.9%)	5.22 (102.6%)
VC (litres)	2.83 (94.3%)	3.76 (125.3%)	3.41 (113.7%)	2.98 (99.3%)	3.17 (105.7%)	3.08 (102.7%)
RV (litres)	2.95 (154.5%)	1.69 (88.5%)	2.07 (108.4%)	2.18 (114.1%)	1.76 (92.2%)	2.14 (112.0%)
RV/TLC (%)	51% (145.7%)	31% (88.6%)	38% (108.6%)	42% (120.0%)	36% (102.9%)	41% (117.1%)
FEV_1 (litres)	2.60 (118.7%)	2.85 (130.1%)	2.50 (114.2%)	2.50 (114.2%)	2.40 (109.6%)	2.00 (91.3%)
FVC (litres)	3.25 (85.8%)	3.70 (97.6%)	3.30 (87.1%)	3.25 (85.8%)	3.30 (87.1%)	2.95 (77.8%)
FEV_1/FVC (%)	80% (102.6%)	77% (98.7%)	76% (97.4%)	77% (98.7%)	73% (93.6%)	68% (86.9%)
$\dot{V}_{max}$ 50 (L/sec)	3.55	3.25	3.26	2.66	2.71	2.34
$\dot{V}_{max}$ 30 (L/sec)	2.32	2.09	1.91	1.90	1.34	1.11
TC_0 (mmol/min/kPa)	6.45 (73.6%)	6.50 (74.2%)	6.57 (75.0%)	7.17 (81.9%)	6.97 (79.6%)	6.67 (76.1%)
sGaw ($sec.^{-1}kPa^{-1}$)	1.392	1.506	1.594	1.246	1.339	1.384
ECG	Normal	Normal	T ↓	T ↓	T ↓	T ↓
Chest x-ray	Normal	Normal	Normal	Normal	Normal	Normal

% Predicted values given in brackets

TABLE 4B

Patient 3

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top 1	71.0	57.0	14.0	30.0	66.0	-36.0	32.0	36.0	-4.0	40.0	40.0	0.0	43.0	56.0	-13.0	64.0	85.0	-21.0
2	57.0	62.0	-5.0	34.0	56.0	-22.0	30.0	41.0	-11.0	38.0	49.0	-11.0	46.0	61.0	-15.0	71.0	69.0	2.0
3	81.0	81.0	0.0	67.0	68.0	-1.0	49.0	52.0	-3.0	65.0	66.0	-1.0	81.0	78.0	3.0	83.0	75.0	8.0
4	100.0	98.0	2.0	99.0	100.0	-1.0	88.0	83.0	5.0	103.0	88.0	15.0	104.0	97.0	7.0	88.0	106.0	-18.0
5	118.0	125.0	-7.0	124.0	129.0	-5.0	127.0	116.0	11.0	127.0	109.0	18.0	129.0	115.0	14.0	114.0	122.0	-8.0
6	129.0	128.0	1.0	146.0	177.0	-31.0	135.0	136.0	-1.0	149.0	127.0	22.0	138.0	133.0	5.0	125.0	133.0	-8.0
7	119.0	105.0	14.0	148.0	178.0	-30.0	160.0	150.0	10.0	146.0	138.0	8.0	137.0	122.0	15.0	119.0	128.0	-9.0
Bottom 8	102.0	86.0	16.0	124.0	155.0	-31.0	133.0	164.0	-31.0	151.0	140.0	11.0	113.0	113.0	0.0	79.0	99.0	-20.0

TABLE 4C

Patient 3

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top 1	2.2	2.2	0.0	2.9	3.9	-1.0	2.2	2.2	0.0	2.1	3.6	-1.5	3.7	3.7	0.0	3.3	2.7	0.6
2	6.1	6.2	-0.1	7.5	8.4	-0.9	5.3	6.3	-1.0	5.9	7.3	-1.4	6.4	7.1	-0.7	5.2	5.1	0.1
3	7.5	7.8	-0.3	8.0	8.8	-0.8	6.9	7.9	-1.0	6.9	8.2	-1.3	7.3	7.5	-0.2	6.5	5.9	0.6
4	8.1	8.7	-0.6	8.6	9.1	-0.5	7.5	8.5	-1.0	7.2	8.3	-1.1	7.1	7.7	-0.6	8.1	6.3	1.8
5	8.5	8.8	-0.3	8.3	9.0	-0.7	7.6	8.6	-1.0	7.1	8.3	-1.2	7.0	7.8	-0.8	7.4	7.2	0.2
6	8.0	8.4	-0.4	6.6	7.4	-0.8	7.7	9.0	-1.3	6.6	8.6	-2.0	7.0	8.0	-1.0	7.4	7.3	0.1
7	5.4	6.3	-0.9	3.7	4.2	-0.5	5.7	7.0	-1.3	6.0	6.4	-0.4	5.5	6.7	-1.2	7.0	5.8	1.2
Bottom 8	2.6	2.9	-0.3	1.6	2.1	-0.5	3.5	4.1	-0.6	3.5	3.9	-0.4	3.4	4.1	-0.7	9.2	5.5	3.7

TABLE 4D

Patient 3

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	46.0	38.0	8.0	86.0	71.0	15.0	54.0	68.0	-14.0	55.0	54.0	1.0	82.0	98.0	-16.0	87.0	72.0	15.0
	2	52.0	60.0	-8.0	95.0	87.0	8.0	78.0	84.0	-6.0	81.0	70.0	11.0	94.0	103.0	-9.0	108.0	75.0	33.0
	3	68.0	76.0	-8.0	108.0	101.0	7.0	89.0	91.0	-2.0	106.0	84.0	22.0	96.0	104.0	-8.0	138.0	84.0	54.0
	4	95.0	81.0	14.0	113.0	108.0	5.0	99.0	103.0	-4.0	119.0	95.0	24.0	97.0	112.0	-15.0	119.0	89.0	30.0
	5	130.0	94.0	36.0	92.0	109.0	-17.0	127.0	109.0	18.0	115.0	101.0	14.0	93.0	115.0	-22.0	127.0	101.0	26.0
	6	155.0	110.0	45.0	103.0	116.0	-13.0	125.0	116.0	9.0	105.0	107.0	-2.0	92.0	115.0	-23.0	112.0	109.0	3.0
	7	192.0	115.0	77.0	98.0	108.0	-10.0	113.0	100.0	13.0	113.0	122.0	-9.0	96.0	103.0	-7.0	106.0	91.0	15.0
Bottom	8	137.0	108.0	29.0	60.0	73.0	-13.0	77.0	76.0	1.0	116.0	127.0	-11.0	67.0	99.0	-32.0	70.0	80.0	-10.0

TABLE 4E

Patient 3

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	77.0	64.0	13.0	73.0	102.0	-29.0	61.0	60.0	1.0	46.0	56.0	-10.0	70.0	62.0	8.0	91.0	97.0	-6.0
	2	85.0	86.0	-1.0	98.0	97.0	1.0	81.0	78.0	3.0	73.0	75.0	-2.0	82.0	80.0	2.0	110.0	99.0	11.0
	3	95.0	91.0	4.0	106.0	114.0	-8.0	98.0	91.0	7.0	102.0	82.0	20.0	88.0	95.0	-7.0	117.0	94.0	23.0
	4	103.0	94.0	9.0	102.0	118.0	-16.0	106.0	105.0	1.0	106.0	92.0	14.0	111.0	104.0	7.0	110.0	97.0	13.0
	5	109.0	107.0	2.0	95.0	115.0	-20.0	111.0	111.0	0.0	112.0	102.0	10.0	123.0	108.0	15.0	131.0	109.0	22.0
	6	111.0	116.0	-5.0	94.0	113.0	-19.0	102.0	109.0	-7.0	116.0	107.0	9.0	120.0	112.0	8.0	109.0	101.0	8.0
	7	118.0	108.0	10.0	84.0	90.4	-6.4	114.0	108.0	6.0	130.0	121.0	9.0	112.0	107.0	5.0	96.0	86.0	10.0
ttom	8	84.0	99.0	-15.0	64.0	68.0	-4.0	93.0	104.0	-11.0	132.0	121.0	11.0	97.0	92.0	5.0	71.0	75.0	-4.0

TABLE 5A

Patient 4

Non-smoker, 43 years. Stage I Anaplastic Carcinoma of Left Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4115 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.70 (108.4%)	5.87 (111.6%)	6.10 (116.0%)	5.28 (100.4%)	5.48 (104.2%)	5.16 (98.1%)
VC (litres)	4.51 (139.6%)	4.05 (125.4%)	3.81 (118.0%)	4.00 (123.8%)	3.83 (118.6%)	3.95 (122.3%)
RV (litres)	1.20 (66.3%)	1.82 (100.6%)	2.29 (126.5%)	1.28 (70.7%)	1.65 (91.2%)	1.21 (66.9%)
RV/TLC (%)	21% (63.5%)	31% (93.9%)	38% (115.2%)	24% (72.7%)	30% (90.9%)	24% (72.7%)
FEV_1 (litres)	3.55 (147.3%)	3.50 (145.2%)	3.07 (127.4%)	3.35 (139.0%)	3.40 (141.1%)	3.25 (134.9%)
FVC (litres)	4.05 (138,2%)	4.10 (139.0%)	3.76 (127.5%)	3.90 (132.2%)	3.95 (133.9%)	3.95 (134.8%)
FEV_1/FVC (%)	88% (110.0%)	85% (106.3%)	82% (102.1%)	86% (107.5%)	86% (107.5%)	82% (102.5%)
$\dot{V}_{max}$ 50 (L/sec)	3.96	4.55	4.75	4.54	4.43	5.21
$\dot{V}_{max}$ 30 (L/sec)	1.48	2.58	2.40	2.35	2.31	2.93
TC_O (mmol/min/kPa)	5.59 (62.5%)	5.96 (66.6%)	6.02 (67.3%)	6.17 (68.9%)	6.00 (67.0%)	6.07 (67.8%)
sGaw ($sec.^{-1}kPa^{-1}$)	1.228	2.051	1.236	2.152	1.910	1.950
ECG	1°H.B.	1°H.B. + T ↓	1°H.B. + T ↓	1°H.B. + T ↓	1°H.B. + T ↓	1°H.B. + T ↓
Chest x-ray	Normal	Normal	Normal	+	+	Normal

% Predicted values given in brackets

TABLE 5B

Patient 4

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Q/E %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	37.0	61.0	-24.0	33.0	68.0	-35.0	33.0	42.0	-9.0	52.0	118.0	-66.0	59.0	84.0	-25.0	38.4	48.8	-10.4
	2	43.0	57.0	-14.0	43.0	65.0	-22.0	43.0	53.0	-10.0	64.0	89.0	-25.0	80.0	86.0	-6.0	44.3	93.0	-48.7
	3	65.0	66.0	-1.0	61.0	82.0	-21.0	76.0	68.0	8.0	83.0	94.0	-11.0	99.0	93.0	6.0	67.9	83.5	-15.6
	4	86.0	94.0	-8.0	81.0	107.0	-26.0	94.0	91.0	3.0	97.0	116.0	-19.0	108.0	104.0	4.0	89.3	92.5	-3.2
	5	105.0	123.0	-18.0	110.0	132.0	-22.0	106.0	119.0	-13.0	99.0	127.0	-28.0	105.0	111.0	-6.0	98.7	100.9	-2.2
	6	129.0	145.0	-16.0	122.0	132.0	-10.0	124.0	143.0	-19.0	106.0	123.0	-17.0	111.0	107.0	5.0	106.3	124.1	-17.8
	7	128.0	159.0	-31.0	132.0	106.0	26.0	144.0	151.0	-7.0	83.0	118.0	-35.0	108.0	97.0	11.0	130.1	133.7	-3.6
ɔttom	8	108.0	142.0	-34.0	157.0	88.0	69.0	141.0	144.0	-3.0	84.0	102.0	-18.0	99.0	94.0	5.0	135.2	144.0	-8.8

TABLE 5C

Patient 4

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	2.7	1.7	1.0	3.5	2.6	0.9	3.7	3.8	-0.1	3.3	2.5	0.8	2.4	2.3	0.1	2.02	2.32	-0.30
	2	6.0	5.8	0.2	5.0	5.4	-0.4	6.3	6.1	0.2	5.9	5.5	0.4	5.4	6.0	-0.6	4.43	5.32	-0.89
	3	7.4	8.2	-0.8	5.7	6.8	-1.1	6.7	7.0	-0.3	7.0	7.1	-0.1	6.6	8.1	-1.5	5.96	6.77	-0.81
	4	7.9	9.6	-1.7	8.0	8.2	-0.2	7.4	8.3	-0.9	7.5	8.0	-0.5	7.7	9.2	-1.5	8.53	9.73	-1.20
	5	7.8	9.9	-2.1	8.7	8.7	0.0	7.6	8.8	-1.2	7.5	8.6	-1.1	7.7	9.6	-1.9	7.74	9.65	-1.91
	6	7.4	9.1	-1.7	7.7	8.7	-1.0	6.9	8.7	-1.8	7.2	8.7	-1.5	6.7	9.3	-2.6	7.52	9.34	-1.82
	7	5.3	5.8	-0.5	6.8	6.6	0.2	5.5	6.4	-0.9	6.4	6.8	-0.4	5.4	6.7	-1.3	5.75	7.36	-1.61
ɔttom	8	2.4	2.6	-0.2	3.9	3.8	0.1	3.2	3.5	-0.3	3.7	4.3	-0.6	2.8	4.1	-1.3	3.48	4.08	-0.60

TABLE 5D

Patient 4

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-Radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	70.0	84.0	-14.0	74.0	113.0	-39.0	86.0	93.0	-7.0	72.0	82.0	-10.0	81.0	83.0	-2.0	89.7	72.1	17.6
	2	82.0	93.0	-11.0	115.0	108.0	7.0	89.0	110.0	-21.0	89.0	88.0	1.0	89.0	94.0	-5.0	102.1	95.3	6.8
	3	95.0	95.0	0.0	132.0	111.0	21.0	103.0	122.0	-19.0	104.0	100.0	4.0	105.0	101.0	4.0	112.4	107.9	4.5
	4	102.0	101.0	1.0	105.0	104.0	1.0	93.0	117.0	-24.0	104.0	105.0	-1.0	98.0	108.0	-10.0	108.4	108.5	-0.1
	5	88.0	101.0	-13.0	85.0	96.0	-11.0	83.0	110.0	-27.0	104.0	103.0	1.0	86.0	102.0	-16.0	86.7	97.6	-10.9
	6	99.0	115.0	-16.0	82.0	90.0	-8.0	89.0	104.0	-15.0	100.0	104.0	-4.0	96.0	108.0	-12.0	90.2	99.0	-8.8
	7	119.0	131.0	-12.0	96.0	94.0	2.0	98.0	95.0	3.0	106.0	103.0	3.0	107.0	107.0	0.0	106.0	104.1	1.9
Bottom	8	101.0	101.0	0.0	115.0	102.0	13.0	90.0	92.0	-2.0	111.0	96.0	15.0	115.0	98.0	17.0	86.1	103.2	-17.1

TABLE 5E

Patient 4

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

	$\dot{V}$/E % (1.5 L/s)	Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	66.0	102.0	-36.0	87.0	97.0	-10.0	82.0	85.0	-3.0	87.0	75.0	12.0	63.0	82.0	-19.0	75.6	73.2	2.4
	2	89.0	109.0	-20.0	106.0	97.0	9.0	90.0	96.0	-6.0	94.0	90.0	4.0	88.0	87.0	1.0	97.8	84.9	12.9
	3	108.0	106.0	2.0	127.0	107.0	20.0	109.0	107.0	2.0	108.0	95.0	13.0	110.0	89.0	21.0	115.6	102.6	13.0
	4	106.0	107.0	-1.0	110.0	104.0	6.0	111.0	108.0	3.0	114.0	103.0	11.0	114.0	89.0	25.0	121.0	110.3	10.7
	5	94.0	102.0	-8.0	97.0	107.0	-10.0	99.0	114.0	-15.0	112.0	100.0	12.0	112.0	99.0	13.0	104.7	98.6	6.1
	6	89.0	102.0	-13.0	96.0	104.0	-8.0	96.0	109.0	-13.0	107.0	99.0	8.0	115.0	108.0	7.0	99.3	105.8	-6.5
	7	94.0	103.0	-9.0	79.0	104.0	-25.0	92.0	99.0	-7.0	104.0	93.0	11.0	108.0	108.0	0.0	92.7	95.4	-2.7
Bottom	8	90.0	88.0	2.0	72.0	80.0	-8.0	70.0	83.0	-13.0	102.0	83.0	19.0	96.0	89.0	7.0	72.3	78.7	-6.4

TABLE 6A

Patient 5

Non-smoker, 59 years. Stage II Poorly Differentiated Adenocarcinoma of Left Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4150 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.01 (103.7%)	4.79 (99.2%)	4.53 (93.8%)	4.86 (100.6%)	4.61 (95.5%)	4.95 (102.5%)
VC (litres)	2.98 (107.6%)	3.00 (108.3%)	2.95 (106.5%)	2.90 (104.7%)	3.00 (108.3%)	3.08 (111.2%)
RV (litres)	2.03 (106.3%)	1.79 (93.7%)	1.58 (82.7%)	1.96 (102.6%)	1.61 (84.3%)	1.87 (97.9%)
RV/TLC (%)	41% (109.9%)	37% (99.2%)	35% (93.8%)	40% (107.2%)	35% (93.8%)	38% (101.9%)
FEV_1 (litres)	2.10 (102.9%)	2.15 (105.4%)	2.00 (98.0%)	2.00 (98.0%)	2.05 (100.5%)	2.20 (107.8%)
FVC (litres)	2.55 (98.0%)	2.80 (109.8%)	2.65 (103.9%)	2.60 (102.0%)	2.80 (109.8%)	2.85 (111.8%)
FEV_1/FVC (%)	84% (109.5%)	76.8% (100.1%)	75.5% (98.4%)	76.9% (100.3%)	73.2% (95.4%)	77.2% (100.7%)
$\dot{V}_{max}$ 50 (L/sec)	2.40	2.09	2.61	2.53	2.57	2.95
$\dot{V}_{max}$ 30 (L/sec)	1.20	0.85	1.18	1.33	1.18	1.29
TC_O (mmol/min/kPa)	6.27 (73.4%)	6.33 (74.1%)	6.51 (76.2%)	5.91 (69.2%)	5.66 (66.3%)	6.17 (72.3%)
sGaw ($sec.^{-1}kPa^{-1}$)	1.139	1.742	1.329	1.526	1.455	1.415
ECG	Normal	Normal	Normal	T ↓	T ↓	Normal
Chest x-ray	Normal	Normal	+	+	Normal	Normal

% Predicted values given in brackets

TABLE 6B

Patient 5

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Q/E %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	112.0	123.0	-11.0	96.0	100.0	-4	85.0	110.0	-25	88.0	103.0	-15	-	-	-	35.5	43.8	-8.3
	2	115.0	124.0	-9.0	101.0	111.0	-10	94.0	111.0	-17	103.0	112.0	-9	-	-	-	48.8	55.4	-6.6
	3	109.0	115.0	-6.0	109.0	110.0	-1	106.0	105.0	1	114.0	108.0	6	-	-	-	77.1	81.1	-4.0
	4	111.0	112.0	-1.0	114.0	113.0	1	102.0	111.0	-9	107.0	117.0	-10	-	-	-	104.3	102.2	2.1
	5	107.0	96.0	11.0	113.0	110.0	3	98.0	114.0	-16	101.0	111.0	-10	-	-	-	123.8	114.8	9.0
	6	90.0	75.0	15.0	110.0	89.0	21	95.0	103.0	-8	79.0	90.0	-11	-	-	-	117.0	137.0	-20.0
	7	68.0	63.0	5.0	83.0	73.0	10	76.0	91.0	-15	75.0	75.0	0	-	-	-	129.7	151.3	-21.6
Bottom	8	66.0	53.0	13.0	73.0	64.0	9	76.0	80.0	-4	78.0	74.0	4	-		-	137.5	130.8	6.7

TABLE 6C

Patient 5

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top 1	4.1	4.6	-0.5	4.0	5.0	-1.0	3.0	2.9	0.1	3.4	3.5	-0.1	-	-	-	2.64	3.35	-0.71
2	6.6	6.7	-0.1	5.6	6.3	-0.7	6.3	6.4	-0.1	5.9	6.7	-0.8	-	-	-	5.56	6.32	-0.76
3	7.3	7.9	-0.6	6.4	7.0	-0.6	7.5	8.2	-0.7	7.6	8.4	-0.8	-	-	-	8.31	10.23	-1.92
4	7.7	9.4	-1.7	7.3	8.0	-0.7	7.9	9.3	-1.4	8.6	9.4	-0.8	-	-	-	7.55	10.46	-2.91
5	7.3	9.5	-2.2	6.8	8.2	-1.4	7.6	9.3	-1.7	8.1	9.8	-1.7	-	-	-	6.60	10.64	-4.04
6	6.3	7.5	-1.2	6.3	8.1	-1.8	6.7	7.7	-1.0	7.4	7.5	-0.1	-	-	-	6.28	8.02	-1.74
7	4.7	4.8	-0.1	6.1	6.3	-0.2	5.6	5.2	0.4	4.4	4.6	-0.2	-	-	-	4.35	4.59	-0.24
Bottom 8	2.5	3.1	-0.6	4.5	4.0	0.5	3.1	3.3	-0.2	2.1	2.6	-0.5	-	-	-	2.41	2.70	-0.29

TABLE 6D

Patient 5

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	88.0	136.0	-48.0	114.0	95.0	19	85.0	81.0	4	65.0	87.0	-22	-	-	-	55.4	56.1	-0.7
	2	107.0	165.0	-58.0	116.0	109.0	7	101.0	101.0	0	89.0	117.0	-28	-	-	-	75.2	80.2	-5.0
	3	128.0	182.0	-54.0	120.0	121.0	-1	113.0	106.0	7	107.0	143.0	-36	-	-	-	95.4	96.9	-1.5
	4	131.0	132.0	-1.0	128.0	127.0	1	120.0	116.0	4	130.0	157.0	-27	-	-	-	108.6	114.2	-5.6
	5	104.0	74.0	30.0	125.0	121.0	4	108.0	129.0	-21	115.0	111.0	4	-	-	-	117.9	129.9	-12.0
	6	59.0	37.0	22.0	107.0	76.0	31	95.0	107.0	-12	72.0	50.0	22	-	-	-	111.2	117.7	-6.5
	7	38.0	27.0	11.0	69.0	41.0	28	74.0	56.0	18	55.0	38.0	17	-	-	-	105.5	77.0	28.5
Bottom	8	33.0	23.0	10.0	48.0	33.0	15	50.0	42.0	8	52.0	37.0	15	-	-	-	78.5	52.6	25.9

TABLE 6E

Patient 5

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	67.0	100.0	-33	105.0	97.0	8	97.0	109.0	-12	84.0	116.0	-32	-	-	-	60.1	62.6	-2.5
	2	91.0	119.0	-28	112.0	117.0	-5	111.0	126.0	-15	116.0	135.0	-19	-	-	-	78.2	85.1	-6.9
	3	101.0	145.0	-44	121.0	125.0	-4	118.0	124.0	-6	123.0	139.0	-16	-	-	-	93.7	98.6	-4.9
	4	112.0	153.0	-41	119.0	115.0	4	114.0	132.0	-18	113.0	141.0	-28	-	-	-	99.1	109.4	-10.3
	5	115.0	123.0	-8	121.0	109.0	12	99.0	126.0	-27	89.0	99.0	-10	-	-	-	116.7	117.5	-0.8
	6	87.0	62.0	25	120.0	77.0	43	78.0	85.0	-7	73.0	56.0	17	-	-	-	99.8	128.2	-28.4
	7	54.0	41.0	13	87.0	43.0	44	50.0	46.0	4	64.0	43.0	21	-	-	-	100.5	95.5	5.0
Bottom	8	44.0	33.0	11	61.0	32.0	39	36.0	39.0	-3	44.0	39.0	5	-	-	-	96.6	73.0	23.5

TABLE 7A

Patient 6

Non-smoker, 47 years. Stage I Mucoid Carcinoma of Left Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4190 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	6.81 (126.4%)	6.53 (121.2%)	5.78 (107.2%)	5.79 (107.4%)	5.74 (106.5%)	5.43 (100.6%)
VC (litres)	4.25 (131.6%)	4.20 (130.0%)	3.95 (122.3%)	3.90 (120.7%)	4.13 (127.9%)	4.10 (127.0%)
RV (litres)	2.56 (130.6%)	2.33 (118.9%)	1.83 (93.4%)	1.89 (96.4%)	1.61 (82.1%)	1.33 (67.9%)
RV/TLC (%)	38% (111.1%)	35.7% (104.4%)	32% (93.6%)	33% (96.5%)	28% (81.9%)	25% (73.1%)
FEV_1 (litres)	3.25 (136.6%)	3.20 (134.5%)	3.20 (134.5%)	3.30 (138.7%)	3.25 (136.6%)	3.25 (136.6%)
FVC (litres)	4.05 (137.3%)	4.05 (137.3%)	4.30 (145.8%)	4.35 (147.5%)	4.00 (135.6%)	4.20 (142.4%)
FEV_1/FVC (%)	80.3% (100.4%)	79% (98.8%)	74% (92.5%)	76% (95.0%)	81% (101.3%)	77% (96.3%)
$\dot{V}_{max}$ 50 (L/sec)	4.54	4.15	3.82	4.80	5.02	4.89
$\dot{V}_{max}$ 30 (L/sec)	1.90	1.60	1.70	1.98	2.11	1.84
TC_O (mmol/min/kPa)	7.86 (86.7%)	6.82 (75.2%)	7.78 (85.8%)	8.04 (88.6%)	6.82 (75.2%)	6.50 (71.7%)
sGaw ($sec.^{-1}kPa^{-1}$)	1.327	1.719	1.104	1.069	1.131	1.126
ECG	Normal	T ↓	T ↓	T ↓	T ↓	T ↓
Chest	Normal	Normal	Normal	Normal	+	+

% Predicted values in brackets

TABLE 7B

Patient 6

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	44.0	56.0	-12.0	38.0	116.9	-78.0	22.0	47.0	-25.0	28.0	36.0	-8.0	68.0	38.0	30.0	80.0	82.7	-2.7
	2	61.0	65.0	-4.0	56.0	68.0	-12.0	36.0	47.0	-11.0	38.0	37.0	1.0	61.0	56.0	5.0	86.0	86.8	-0.8
	3	85.0	85.0	0.0	83.0	90.0	-7.0	75.0	68.0	7.0	66.0	61.0	5.0	81.0	70.0	11.0	109.8	105.3	4.5
	4	108.0	101.0	7.0	96.0	105.0	-9.0	123.0	89.0	34.0	97.0	85.0	12.0	101.0	86.0	15.0	114.0	123.5	-9.5
	5	117.0	126.0	-9.0	120.0	115.0	5.0	123.0	104.0	19.0	120.0	111.0	9.0	116.0	104.0	12.0	110.6	106.1	4.5
	6	114.0	127.0	-13.0	121.0	117.0	4.0	141.0	124.0	17.0	135.0	144.0	-9.0	122.0	122.0	0.0	98.4	98.4	0.0
	7	115.0	127.0	-12.0	121.0	107.0	14.0	155.0	133.0	22.0	149.0	164.0	-15.0	124.0	124.0	0.0	100.8	75.7	25.1
Bottom	8	114.0	123.0	-9.0	107.0	96.0	11.0	164.0	115.0	49.0	133.0	144.0	-11.0	134.0	123.0	11.0	83.1	70.4	13.7

TABLE 7C

Patient 6

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	4.2	4.6	-0.4	2.3	4.2	-1.9	2.2	3.6	-1.4	3.7	2.2	1.5	2.1	2.7	-0.6	2.15	2.61	-0.46
	2	5.8	6.3	-0.5	5.3	7.1	-1.8	6.1	6.6	-0.5	6.0	5.9	0.1	5.0	5.1	-0.1	5.30	6.29	-0.99
	3	6.4	7.7	-1.3	6.8	8.0	-1.2	6.5	7.9	-1.4	7.0	7.1	-0.1	6.6	6.5	0.1	6.01	7.18	-1.17
	4	7.1	9.3	-2.2	7.5	9.0	-1.5	6.4	9.1	-2.7	7.5	8.7	-1.2	7.7	8.4	-0.7	6.77	8.33	-1.56
	5	7.1	9.1	-2.0	6.9	9.2	-2.3	6.9	9.4	-2.5	7.7	9.6	-1.9	7.8	9.3	-1.5	8.66	11.83	-3.17
	6	6.8	7.8	-1.0	6.5	8.3	-1.8	6.0	8.7	-2.7	7.3	8.1	-0.8	7.6	8.7	-1.1	7.05	8.34	-1.29
	7	5.4	5.3	0.1	5.3	6.1	-0.8	5.5	6.4	-0.9	6.1	5.6	0.5	6.7	7.0	-0.3	5.79	6.65	-0.86
Bottom	8	3.9	3.2	0.7	3.4	4.0	-0.6	3.9	4.7	-0.8	4.1	3.5	0.6	4.6	4.2	0.4	3.75	3.26	-0.49

TABLE 7D

Patient 6

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	96.0	73.0	23	67.0	56.0	11	65.0	77.0	-12	100.0	51.0	49	85.0	85.0	0	84.7	97.5	-12.8
	2	112.0	86.0	26	71.0	78.0	-7	82.0	90.0	-8	103.0	75.0	28	96.0	108.0	-12	107.1	103.3	3.8
	3	121.0	94.0	27	79.0	96.0	-17	108.0	102.0	6	122.0	90.0	32	105.0	104.0	1	111.9	111.0	0.9
	4	116.0	91.0	25	92.0	110.0	-18	124.0	115.0	9	126.0	94.0	32	106.0	107.0	-1	124.9	116.9	8.0
	5	105.0	96.0	9	111.0	115.0	-4	110.0	124.0	-14	114.0	91.0	23	105.0	112.0	-7	122.2	107.6	14.6
	6	101.0	96.0	5	123.0	127.0	-4	117.0	123.0	-6	114.0	99.0	15	96.0	105.0	-9	104.9	90.7	14.2
	7	109.0	108.0	1	115.0	130.0	-15	86.0	81.0	5	114.0	93.0	21	91.0	92.0	-1	78.3	59.3	19.0
Bottom	8	93.0	105.0	-12	69.0	92.0	-13	55.0	46.0	9	80.0	77.0	3	81.0	82.0	-1	57.3	49.9	7.4

TABLE 7E

Patient 6

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	72.0	98.0	-26	116.0	131.0	-15	58.0	58.0	0	81.0	51.0	30	90.0	87.0	3	92.7	95.1	-2.4
	2	85.0	100.0	-15	138.0	132.0	6	79.0	73.0	6	102.0	74.0	28	108.0	102.0	6	108.4	106.9	1.5
	3	106.0	100.0	6	138.0	148.0	-10	115.0	87.0	28	125.0	89.0	36	112.0	106.0	6	119.2	111.4	6.8
	4	123.0	103.0	20	131.0	160.0	-29	123.0	95.0	28	125.0	96.0	29	111.0	110.0	1	120.6	117.6	3.0
	5	124.0	111.0	13	97.0	118.0	-21	107.0	102.0	5	113.0	94.0	19	109.0	104.0	5	106.6	109.4	-2.8
	6	109.0	99.0	10	44.0	55.0	-11	117.0	107.0	10	117.0	101.0	16	96.0	100.0	-4	90.7	97.3	-6.6
	7	89.0	95.0	-6	26.0	27.0	-1	114.0	110.0	4	111.0	97.0	14	95.0	86.0	9	78.2	69.7	8.5
Bottom	8	63.0	67.0	-4	22.0	24.0	-2	110.0	111.0	0	81.0	77.0	4	73.0	77.0	-4	56.6	59.2	-2.6

TABLE 8A

Patient 7

Smoker, 57 years. Stage III Invasive Carcinoma of Right Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 3910 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.72 (109.4%)	5.42 (103.6%)	5.97 (114.2%)	5.08 (97.1%)	5.14 (98.3%)	5.22 (99.8%)
VC (litres)	2.26 (74.8%)	2.40 (79.5%)	2.27 (75.2%)	2.14 (70.9%)	2.02 (66.9%)	2.08 (68.9%)
RV (litres)	3.46 (168.8%)	3.03 (147.3%)	3.70 (180.5%)	2.98 (145.4%)	3.12 (152.2%)	3.14 (153.2%)
RV/TLC (%)	61% (165.8%)	56% (152.2%)	62% (186.5%)	58% (157.6%)	61% (165.8%)	60% (163.0%)
FEV_1 (litres)	1.50 (70.8%)	1.35 (63.7%)	1.20 (56.6%)	1.05 (49.5%)	1.05 (49.5%)	1.05 (49.5%)
FVC (litres)	1.70 (63.7%)	2.00 (74.9%)	1.75 (65.5%)	1.35 (50.6%)	1.80 (67.4%)	1.55 (58.1%)
FEV_1/FVC (%)	88% (110.0%)	68% (85.0%)	69% (86.3%)	78% (97.5%)	58% (72.5%)	68% (85.0%)
$\dot{V}_{max}$ 50 (L/sec)	1.68	1.10	0.93	1.32	1.25	1.33
$\dot{V}_{max}$ 30 (L/sec)	0.95	0.50	0.45	0.67	0.61	0.54
TC_O (mmol/min/kPa)	5.77 (63.6%)	6.58 (72.6%)	6.91 (76.2%)	6.46 (71.2%)	6.00 (66.2%)	6.17 (68.0%)
sGaw ($sec.^{-1}kPa^{-1}$)	0.676	0.725	0.749	0.775	0.683	0.540
ECG	Normal	Normal	Normal	Normal	Normal	Normal
Chest x-ray	Normal	Normal	Normal	+	+	+

% Predicted values in brackets

TABLE 8B

Patient 7

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	102.0	160.0	-58	97.0	109.0	-12	113.0	146.0	-33	131.0	150.0	-19	161.0	150.0	11	53.3	94.7	-41.4
	2	89.0	126.0	-37	89.0	91.0	-2	117.0	123.0	-6	116.0	123.0	-7	104.0	115.0	-11	64.2	111.4	-47.2
	3	102.0	111.0	-9	95.0	82.0	13	125.0	97.0	28	107.0	112.0	-5	104.0	81.0	23	86.9	89.3	-2.4
	4	108.0	107.0	1	109.0	94.0	15	126.0	101.0	25	110.0	107.0	3	98.0	73.0	25	110.5	87.9	22.6
	5	113.0	106.0	7	109.0	105.0	4	118.0	101.0	17	109.0	101.0	8	108.0	87.0	21	117.4	97.7	19.7
	6	83.0	98.0	-15	102.0	107.0	-5	77.0	88.0	-11	92.0	92.0	0	112.0	86.0	26	127.1	106.2	20.9
	7	66.0	77.0	-11	106.0	98.0	8	67.0	78.0	-11	80.0	83.0	-3	105.0	98.0	7	116.7	105.0	11.7
Bottom	8	53.0	83.0	-30	102.0	100.0	2	56.0	71.0	-15	77.0	69.0	8	136.0	128.0	8	105.9	114.0	-8.1

TABLE 8C

Patient 7

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	4.2	3.7	0.5	3.1	2.4	0.7	2.8	2.3	0.5	1.0	2.2	-1.2	1.3	1.7	-0.4	3.42	3.33	0.09
	2	6.9	5.8	1.1	5.9	5.1	0.8	5.5	5.2	0.3	4.3	4.8	-0.5	4.1	4.1	0.0	4.76	5.25	-0.49
	3	7.9	7.1	0.8	7.9	6.9	1.0	7.1	7.4	-0.3	6.7	6.8	-0.1	6.1	9.5	-3.4	8.17	8.21	-0.04
	4	9.0	7.4	1.6	8.9	7.9	1.0	8.2	8.1	0.1	8.0	7.8	0.2	8.0	9.6	-1.6	9.56	9.29	0.27
	5	9.1	7.5	1.6	9.7	8.2	1.5	9.0	8.7	0.3	9.1	8.0	1.1	9.1	9.6	-0.5	9.22	9.04	0.18
	6	8.7	6.6	2.1	9.0	7.7	1.3	9.8	7.4	2.4	9.1	8.3	0.8	8.8	9.0	-0.2	6.24	6.16	0.08
	7	6.1	4.4	1.7	5.9	5.4	0.5	6.7	4.9	1.8	7.2	7.2	0.0	7.5	6.6	0.9	5.36	5.83	-0.47
Bottom	8	3.6	2.2	1.4	3.3	2.9	0.4	3.8	3.1	0.7	4.6	4.9	-0.3	3.8	3.3	0.5	2.47	3.67	-1.20

TABLE 8D

Patient 7

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	66.0	99.0	-33	95.0	144.0	-49	96.0	100.0	-4	135.0	121.0	14	57.0	72.0	-15	66.0	70.0	-4.4
	2	89.0	130.0	-41	103.0	147.0	-44	111.0	128.0	-17	136.0	146.0	-10	68.0	94.0	-26	88.0	101.3	-13.3
	3	113.0	115.0	-2	103.0	129.0	-26	118.0	115.0	-3	121.0	135.0	-14	100.0	110.0	-10	103.0	103.3	-0.3
	4	114.0	97.0	17	116.0	117.0	-1	131.0	105.0	26	113.0	114.0	-1	119.0	105.0	14	129.7	89.5	40.2
	5	131.0	93.0	38	115.0	101.0	14	131.0	98.0	33	102.0	107.0	-5	125.0	107.0	18	135.9	87.1	48.8
	6	110.0	87.0	23	84.0	77.0	7	94.0	84.0	10	81.0	92.0	-11	118.0	94.0	24	119.4	92.5	26.9
	7	85.0	68.0	17	72.0	65.0	7	62.0	63.0	-1	60.0	75.0	-15	80.0	87.0	-7	104.3	87.7	16.6
Bottom	8	53.0	58.0	-5	47.0	49.0	-2	46.0	49.0	-3	51.0	63.0	-12	75.0	75.0	0	69.9	66.8	3.1

TABLE 8E

Patient 7

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	168.0	170.0	-2	156.0	192.0	-36	165.0	156.0	9	133.0	125.0	8	66.0	106.0	-40	115.4	115.7	-0.3
	2	143.0	157.0	-14	137.0	161.0	-24	168.0	153.0	15	118.0	138.0	-20	82.0	121.0	-39	129.5	140.6	-11.1
	3	135.0	99.0	36	120.0	136.0	-16	155.0	120.0	35	120.0	130.0	-10	96.0	125.0	-29	118.5	116.8	1.7
	4	136.0	89.0	47	124.0	123.0	1	161.0	113.0	48	123.0	98.0	25	97.0	118.0	-21	128.9	97.7	31.2
	5	109.0	71.0	38	98.0	93.0	5	110.0	95.0	15	116.0	89.0	27	106.0	117.0	-11	108.2	85.8	22.4
	6	71.0	52.0	19	70.0	61.0	9	50.0	58.0	-8	98.0	78.0	20	105.0	99.0	6	91.9	83.0	8.9
	7	50.0	34.0	16	42.0	44.0	-2	35.0	47.0	-12	79.0	71.0	8	68.0	88.0	-20	65.3	56.0	9.3
Bottom	8	32.0	34.0	-2	31.0	33.0	-2	31.0	41.0	-10	62.0	66.0	-4	59.0	69.0	-10	41.6	50.6	-9.0

TABLE 9A

Patient 8

Non-smoker, 50 years. Stage II Undifferentiated Scirrhous Carcinoma of Right Breast
Treated by Simple Mastectomy Followed by Radiotherapy
(Maximum dose 4250 rads : Minimum central dose 4115 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.80 (109.4%)	5.93 (111.1%)	5.60 (104.9%)	5.42 (101.5%)		
VC (litres)	4.05 (127.8%)	4.08 (128.7%)	4.03 (127.1%)	3.85 (121.5%)		
RV (litres)	1.79 (164.2%)	1.85 (169.7%)	1.57 (144.0%)	1.57 (144.0%)		
RV/TLC (%)	31% (88.6%)	31% (88.6%)	28% (80.0%)	29% (82.9%)		
FEV_1 (litres)	2.95 (126.6%)	3.00 (128.8%)	2.85 (122.3%)	2.90 (124.5%)		
FVC (litres)	4.00 (137.5%)	4.20 (144.3%)	3.95 (135.7%)	4.00 (137.5%)	Patient Developed Liver Metastases	
FEV_1/FVC (%)	74% (93.7%)	71% (89.9%)	72% (91.1%)	72% (91.1%)		
$\dot{V}max$ 50 (L/sec)	3.08	3.22	3.23	3.41		
$\dot{V}max$ 30 (L/sec)	1.38	1.75	1.65	1.75		
TC_O (mmol/min/kPa)	9.08 (100.6%)	8.65 (95.8%)	7.65 (84.7%)	7.22 (80.0%)		
sGaw ($sec.^{-1}kPa^{-1}$)	0.920	1.157	1.139	1.105		
ECG	Normal	Normal	Normal	Normal		
Chest x-ray	Normal	Normal	+	+		

% Predicted values in brackets

TABLE 9B

Patient 8

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-Radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	47.0	57.0	-10.0	40.0	65.0	-25.0	33.0	56.0	-23.0	46.0	74.0	-28.0						
	2	58.0	66.0	-8.0	56.0	81.0	-25.0	47.0	62.0	15.0	51.0	67.0	-16.0						
	3	78.0	82.0	-4.0	87.0	97.0	-10.0	66.0	87.0	-21.0	70.0	89.0	-19.0						
	4	95.0	94.0	1.0	101.0	99.0	2.0	96.0	108.0	-12.0	90.0	103.0	-13.0	Patient Developed Liver Metastases					
	5	115.0	104.0	11.0	112.0	110.0	2.0	115.0	130.0	-15.0	110.0	117.0	-7.0						
	6	118.0	117.0	1.0	131.0	113.0	18.0	133.0	119.0	14.0	119.0	124.0	-5.0						
	7	120.0	123.0	-3.0	114.0	107.0	7.0	119.0	122.0	-3.0	125.0	124.0	1.0						
Bottom	8	129.0	130.0	-1.0	116.0	97.0	19.0	100.0	104.0	-4.0	98.0	100.0	-2.0						

TABLE 9C

Patient 8

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	2.3	3.3	-1.0	1.8	4.2	-2.4	2.0	3.6	-1.6	1.9	2.7	-0.8						
	2	5.1	5.9	-0.8	5.1	6.3	-1.2	4.9	6.1	-1.2	4.9	5.5	-0.6						
	3	6.4	6.9	-0.5	6.3	7.2	-0.9	5.9	7.2	-1.3	6.3	6.7	-0.4						
	4	7.4	7.2	0.2	7.6	8.1	-0.5	6.7	8.0	-1.3	7.3	7.9	-0.6	Patient Developed Liver Metastases					
	5	7.7	7.8	-0.1	8.2	7.8	0.4	7.3	7.7	-0.4	7.9	8.1	-0.2						
	6	7.9	7.4	0.5	7.4	7.6	-0.2	7.5	8.3	-0.8	8.4	7.7	0.7						
	7	7.2	6.9	0.3	6.9	6.8	0.1	6.9	7.5	-0.6	6.8	7.3	-0.5						
Bottom	8	5.3	5.3	0.0	4.2	4.4	-0.2	4.9	5.3	-0.4	5.0	5.7	-0.7						

TABLE 9D

Patient 8

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	58.0	61.0	-3	74.0	68.0	6	52.0	67.0	-15	61.0	69.0	-8						
	2	80.0	84.0	-4	83.0	85.0	-2	71.0	83.0	-12	69.0	80.0	-11						
	3	98.0	97.0	1	96.0	91.0	5	85.0	99.0	-14	80.0	99.0	-19						
	4	95.0	112.0	-17	92.0	88.0	4	104.0	110.0	-6	97.0	101.0	-4	Patient Developed Liver Metastases					
	5	109.0	108.0	1	101.0	90.0	11	110.0	109.0	1	106.0	107.0	-1						
	6	101.0	111.0	-10	117.0	106.0	11	124.0	94.0	30	106.0	105.0	1						
	7	104.0	108.0	-4	112.0	125.0	-13	129.0	96.0	33	134.0	102.0	32						
Bottom	8	107.0	113.0	- 6	124.0	136.0	-12	127.0	76.0	51	129.0	96.0	33						

TABLE 9E

Patient 8

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	61.0	71.0	-10	97.0	99.0	-2	82.0	82.0	0	88.0	81.0	7						
	2	79.0	87.0	-8	98.0	98.0	0	100.0	94.0	6	98.0	90.0	8						
	3	89.0	109.0	-20	101.0	102.0	-1	111.0	103.0	8	98.0	100.0	-2						
	4	99.0	117.0	-18	95.0	97.0	-2	115.0	107.0	8	103.0	100.0	3	Patient Developed Liver Metastases					
	5	110.0	112.0	-2	96.0	101.0	-5	119.0	111.0	8	107.0	104.0	3						
	6	101.0	105.0	-4	107.0	102.0	5	121.0	87.0	34	112.0	99.0	13						
	7	103.0	93.0	10	105.0	100.0	5	114.0	76.0	38	121.0	89.0	32						
Bottom	8	109.0	105.0	4	103.0	97.0	6	83.0	61.0	22	97.0	82.0	15						

TABLE 10A

Patient 9

Non-smoker, 42 years. Stage I Adenocarcinoma of Left Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4000 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.47 (95.0%)	4.70 (81.6%)	4.78 (83.0%)	5.10 (88.5%)	4.76 (82.6%)	5.42 (94.0%)
VC (litres)	3.88 (110.5%)	3.53 (100.6%)	3.53 (100.6%)	3.73 (106.3%)	3.75 (106.8%)	3.70 (105.0%)
RV (litres)	1.59 (77.6%)	1.71 (57.1%)	1.25 (61.0%)	1.37 (66.8%)	1.01 (49.3%)	1.72 (84.0%)
RV/TLC (%)	98.4% (118.7%)	82.9% (100.0%)	82.9% (100.0%)	91% (112.4%)	21% (64.0%)	32% (98.0%)
FEV_1 (litres)	3.05 (117.8%)	3.15 (121.6%)	2.90 (112.0%)	3.20 (123.6%)	3.00 (115.8%)	3.00 (116.0%)
FVC (litres)	3.10 (95.7%)	3.80 (117.3%)	3.50 (108.0%)	3.50 (108.0%)	3.55 (109.6%)	3.65 (113.0%)
FEV_1/FVC (%)	29% (88.4%)	25% (76.2%)	26% (79.3%)	37% (112.8%)	85% (104.9%)	82% (101.0%)
$\dot{V}_{max}$ 50 (L/sec)	4.16	4.91	4.79	4.02	4.71	4.09
$\dot{V}_{max}$ 30 (L/sec)	2.50	2.45	2.67	2.62	2.39	2.31
TC_0 (mmol/min/kPa)	6.71 (91.5%)	6.75 (92.1%)	6.48 (88.4%)	6.80 (92.8%)	7.43 (101.4%)	7.52 (103.0%)
sGaw ($sec.^{-1}kPa^{-1}$)	1.478	1.600	1.885	1.462	1.847	1.402
ECG	Normal	Normal	T ↓	T ↓	T ↓	T ↓
Chest x-ray	Normal	Normal	Normal	Normal	Normal	Normal

% Predicted values in brackets

TABLE 10B

Patient 9

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

	$\dot{Q}/E$ %	Control			1 month			3 months			6 months			9 month			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	105.0	115.0	-10.0	109.0	84.0	25.0	82.0	95.0	-13.0	64.3	82.3	-18.0	66.8	61.2	5.6	96.0	118.7	-22.7
	2	89.0	85.0	4.0	106.0	85.0	21.0	103.0	80.0	23.0	96.0	79.6	16.4	75.7	65.0	10.7	101.5	105.6	-4.1
	3	103.0	82.0	21.0	111.0	97.0	14.0	114.0	93.0	21.0	111.0	101.6	9.4	104.9	77.7	27.2	120.6	118.9	1.7
	4	101.0	94.0	7.0	112.0	98.0	14.0	111.0	97.0	14.0	119.1	108.8	10.3	129.7	104.6	25.1	132.1	123.3	8.8
	5	116.0	99.0	17.0	112.0	103.0	9.0	113.0	106.0	7.0	102.7	90.1	12.6	131.9	100.6	31.3	130.6	113.8	16.8
	6	125.0	91.0	34.0	114.0	96.0	18.0	112.0	102.0	10.0	120.1	101.6	18.5	126.8	106.2	20.6	96.7	80.9	15.8
	7	111.0	95.0	16.0	96.0	92.0	4.0	93.0	98.0	-5.0	109.1	105.7	3.4	116.7	93.0	23.7	66.9	67.1	-0.2
Bottom	8	103.0	98.0	5.0	82.0	71.0	11.0	83.0	89.0	-6.0	75.6	76.9	-1.3	113.6	88.4	25.2	30.3	36.9	-6.6

TABLE 10C

Patient 9

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	1.2	0.5	0.7	1.5	1.4	0.1	2.9	2.9	0.0	2.67	1.96	0.71	4.0	3.3	0.7	3.8	3.9	-0.1
	2	3.7	3.9	-0.2	4.5	5.5	-1.0	5.3	6.5	-1.2	5.40	5.66	-0.26	5.2	5.1	0.1	5.8	6.2	-0.4
	3	6.0	7.3	-1.3	6.7	7.5	-0.8	6.5	7.9	-1.4	6.96	7.27	-0.31	7.3	8.2	-0.9	6.5	7.7	-1.2
	4	8.3	8.8	-0.5	8.1	8.6	-0.5	7.2	9.2	-2.0	7.08	8.85	-1.77	5.6	7.3	-1.7	5.6	7.3	-1.7
	5	7.8	9.7	-1.9	8.4	9.6	-1.2	7.0	9.6	-2.6	7.94	11.88	-3.94	7.3	10.5	-3.2	7.2	9.9	-2.7
	6	7.3	10.2	-2.9	7.7	9.6	-1.9	6.7	8.9	-2.2	6.12	9.66	-3.54	6.8	9.7	-2.9	7.3	9.5	-2.2
	7	7.1	8.1	-1.0	6.2	6.5	-0.3	5.5	6.0	-0.5	4.76	7.08	-2.32	4.6	5.9	-1.3	5.3	6.7	-1.4
Bottom	8	4.9	5.2	-0.3	4.0	4.3	-0.3	3.6	4.1	-0.5	2.80	3.93	-1.13	4.1	4.9	-0.8	3.2	4.2	-1.0

TABLE 10D

Patient 9

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}/E$ % (0.2 L/s)	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top 1	67.0	55.0	12	75.0	70.0	5	80.0	74.0	6	85.8	69.8	-16.0	69.9	62.2	7.7	58.1	79.3	-21.2
2	76.0	75.0	1	101.0	97.0	4	132.0	104.0	28	84.2	90.7	-6.5	83.5	74.7	8.8	74.3	101.3	-27.0
3	98.0	96.0	2	123.0	116.0	7	142.0	113.0	29	99.5	97.9	1.6	96.3	81.8	14.5	82.1	112.6	-30.5
4	103.0	106.0	-3	114.0	109.0	5	135.0	111.0	24	102.7	113.9	-11.2	104.6	96.1	5.5	89.6	114.5	-24.9
5	112.0	107.0	5	107.0	111.0	-4	122.0	108.0	14	103.6	111.1	-7.5	100.9	100.5	0.4	92.4	120.2	-27.8
6	112.0	104.0	8	107.0	90.0	17	89.0	86.0	3	100.1	118.2	-18.1	106.9	114.4	-7.5	90.4	121.5	-31.1
7	100.0	102.0	-2	87.0	79.0	8	63.0	69.0	-6	98.4	105.4	-7.0	123.4	123.1	0.3	106.6	124.0	-17.4
Bottom 8	97.0	85.0	12	68.0	65.0	3	41.0	47.0	-6	81.4	85.9	-4.5	111.2	115.9	-4.7	83.2	82.6	-1.4

TABLE 10E

Patient 9

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	94.0	96.0	-2	102.0	107.0	-5	108.0	104.0	4	137.4	107.6	29.8	71.2	79.9	-8.7	94.3	98.6	-4.3
	2	84.0	107.0	-23	126.0	128.0	-2	146.0	121.0	25	113.4	112.5	0.9	87.4	85.0	2.4	114.1	114.9	-0.8
	3	106.0	124.0	-18	137.0	135.0	2	139.0	115.0	24	105.5	106.0	-0.5	102.5	89.5	3.0	122.8	111.5	11.3
	4	97.0	114.0	-17	117.0	116.0	1	118.0	109.0	9	105.8	108.6	-2.8	107.8	95.5	12.3	116.3	106.5	9.8
	5	97.0	110.0	-13	107.0	106.0	1	103.0	99.0	4	103.9	108.0	-4.1	102.7	98.3	4.4	108.2	107.3	0.9
	6	103.0	104.0	-1	86.0	75.0	11	93.0	79.0	14	90.1	105.7	-15.6	112.1	111.0	1.1	97.3	92.4	4.9
	7	93.0	89.0	4	70.0	65.0	5	68.0	65.0	3	72.9	85.4	-12.5	114.2	122.7	-8.5	86.1	73.5	12.6
Bottom	8	70.0	76.0	-6	47.0	52.0	-5	48.0	47.0	1	64.2	72.1	-7.9	93.7	103.1	-9.4	59.5	57.0	2.5

TABLE 11A

Patient 10

Non-smoker, 35 years. Stage I Intraduct Carcinoma of Left Breast - Treated by Simple Mastectomy Followed by Radiotherapy

(Maximum dose 4250 rads : Minimum central dose 4135 rads)

Overall Lung Function Measurements	Control	1 month	3 months	6 months	9 months	12 months
TLC (litres)	5.02 (105.2%)	4.81 (100.8%)	4.77 (100.0%)	4.61 (96.6%)	4.61 (96.6%)	4.68 (98.0%)
VC (litres)	3.78 (125.2%)	3.50 (115.9%)	3.40 (112.6%)	3.30 (97.0%)	3.40 (100.0%)	3.28 (109.0%)
RV (litres)	1.24 (82.1%)	1.31 (86.8%)	1.37 (90.7%)	1.31 (95.6%)	1.21 (88.3%)	1.40 (93.0%)
RV/TLC (%)	25% (80.6%)	27% (87.1%)	29% (93.5%)	28% (90.3%)	26% (83.3%)	30% (97.0%)
FEV_1 (litres)	3.40 (143.5%)	3.30 (139.2%)	3.30 (139.2%)	3.05 (128.7%)	3.20 (135.0%)	3.15 (133.0%)
FVC (litres)	3.80 (136.2%)	3.65 (130.8%)	3.50 (125.5%)	3.45 (123.7%)	3.50 (125.5%)	3.40 (122.0%)
FEV_1/FVC (%)	89.5% (107.8%)	90.5% (108.9%)	94.3% (113.6%)	88.4% (106.5%)	91% (109.6%)	93% (110.0%)
$\dot{V}_{max}$ 50 (L/sec)	5.15	5.11	4.88	4.79	3.95	4.33
$\dot{V}_{max}$ 30 (L/sec)	2.94	2.67	2.86	2.70	2.22	2.49
TC_0 (mmol/min/kPa)	7.48 (88.1%)	6.93 (81.6%)	6.15 (72.4%)	7.28 (85.2%)	7.35 (86.6%)	6.89 (81.0%)
sGaw ($sec.^{-1}kPa^{-1}$)	1.640	1.223	1.464	1.501	1.703	1.314
ECG	Normal	T ↓	T ↓	T ↓	T ↓	T ↓
Chest x-ray	Normal	Normal	Normal	Normal	+	+

% Predicted values in brackets

TABLE 11B

Patient 10

Perfusion/Unit Alveolus % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{Q}/E$ %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	53.0	56.0	-3.0	64.0	73.0	-9.0	27.0	34.0	-7.0	58.9	72.4	-13.5	66.5	91.2	-24.7	77.0	105.9	-28.9
	2	60.0	59.0	1.0	59.0	76.0	-17.0	33.0	49.0	-16.0	55.3	67.3	-12.0	72.1	64.3	7.8	69.0	74.3	-5.3
	3	76.0	73.0	3.0	86.0	69.0	17.0	54.0	53.0	1.0	71.0	84.9	-13.9	93.7	90.6	3.1	92.6	91.8	0.8
	4	100.0	90.0	10.0	100.0	88.0	12.0	84.0	84.0	0.0	96.0	102.1	-6.1	98.3	114.8	-16.5	110.4	120.8	-10.4
	5	113.0	104.0	9.0	101.0	100.0	1.0	106.0	110.0	-4.0	101.2	121.1	-19.9	111.1	124.9	-13.8	111.7	124.3	-12.6
	6	127.0	124.0	3.0	118.0	112.0	6.0	118.0	139.0	-21.0	113.5	134.2	-20.7	117.3	124.9	-7.6	115.3	129.5	-14.2
	7	133.0	141.0	-8.0	138.0	134.0	4.0	142.0	165.0	-23.0	124.0	126.1	-2.1	100.5	110.3	-9.8	100.1	114.7	-14.6
Bottom	8	159.0	140.0	19.0	140.0	110.0	30.0	183.0	198.0	-15.0	104.4	95.2	9.2	72.1	57.1	15.0	37.1	36.7	0.4

TABLE 11C

Patient 10

Lung Volumes % in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

Lung Volume %		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	3.3	3.9	-0.6	3.9	3.1	0.8	3.6	2.0	1.6	3.03	3.15	-0.12	3.0	3.6	-0.6	3.1	3.3	-0.2
	2	5.9	6.4	-0.5	6.7	5.1	1.6	6.0	5.3	0.7	5.51	5.35	0.15	5.0	5.9	-0.9	5.6	5.8	-0.2
	3	7.8	7.3	0.5	7.2	6.2	1.0	8.1	6.9	1.2	6.89	7.03	-0.14	7.3	9.1	-1.8	7.7	8.5	-0.8
	4	8.1	7.9	0.2	7.5	7.0	0.5	8.3	7.4	0.9	7.25	8.13	-0.88	6.6	8.3	-1.7	6.6	7.7	-1.1
	5	7.5	8.2	-0.7	7.4	7.2	0.2	7.7	7.8	-0.1	7.67	8.36	-0.69	7.8	10.3	-2.5	6.6	8.3	-1.7
	6	6.9	7.5	-0.6	7.0	7.0	0.0	7.6	7.7	-0.1	7.13	7.82	-0.69	6.0	7.8	-1.8	7.6	9.4	-1.8
	7	5.9	6.0	-0.1	6.9	5.8	1.1	6.6	6.7	-0.1	7.66	8.24	-0.58	6.3	7.3	-1.0	5.8	6.4	-0.6
Bottom	8	3.7	3.8	-0.1	7.1	4.8	2.3	4.3	3.9	0.4	3.96	2.83	1.13	2.7	3.1	-0.4	3.6	4.2	-0.6

TABLE 11D

Patient 10

Ventilation/Unit Alveolus % (0.2 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (0.2 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	104.0	95.0	9	87.0	91.0	-4	58.0	89.0	-31	53.1	58.2	-5.1	55.7	60.1	-4.4	66.8	77.3	-10.5
	2	111.0	102.0	9	90.0	115.0	-25	77.0	113.0	-36	66.2	71.7	-5.5	68.7	84.4	-15.7	84.0	90.1	-6.1
	3	107.0	113.0	-6	107.0	115.0	-8	96.0	112.0	-16	89.6	83.9	5.7	79.0	88.6	-9.6	99.1	99.3	-0.2
	4	106.0	119.0	-13	108.0	104.0	4	101.0	124.0	-23	108.8	93.1	15.7	94.0	97.6	1.8	110.5	117.0	-6.5
	5	84.0	114.0	-30	94.0	109.0	-15	98.0	120.0	-22	117.0	108.3	8.7	112.3	104.8	7.5	118.4	115.2	3.2
	6	70.0	112.0	-42	81.0	107.0	-26	82.0	116.0	-34	123.2	110.8	12.4	124.1	112.3	11.8	93.4	109.0	-15.6
	7	62.0	113.0	-51	92.0	118.0	-26	78.0	110.0	-32	110.4	108.0	2.4	125.1	118.6	6.5	81.5	111.1	-29.6
Bottom	8	58.0	100.0	42	79.0	101.0	-22	83.0	108.0	-25	130.2	125.9	4.3	122.4	120.5	1.9	79.1	92.3	-13.2

TABLE 11E

Patient 10

Ventilation/Unit Alveolus % (1.5 L/s) in 8 Vertical Slices (Top to Bottom) of the Lung at Pre-radiotherapy (Control) and at Different Intervals After Radiotherapy

$\dot{V}$/E % (1.5 L/s)		Control			1 month			3 months			6 months			9 months			12 months		
		Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
Top	1	81.0	80.0	1	102.0	87.0	15	71.0	67.0	4	117.4	101.2	16.2	116.1	135.7	-19.6	90.2	92.2	-2.0
	2	91.0	91.0	0	88.0	102.0	-14	82.0	88.0	-6	109.0	99.9	9.1	112.8	122.2	-9.4	98.8	102.9	-4.1
	3	82.0	99.0	-17	117.0	95.0	22	99.0	94.0	5	111.0	92.9	18.1	105.1	118.2	-13.1	101.7	105.4	-3.7
	4	98.0	102.0	-4	110.0	92.0	18	111.0	98.0	13	117.6	92.4	25.2	102.2	126.0	-23.8	107.7	103.2	4.5
	5	106.0	107.0	-1	103.0	104.0	-1	123.0	101.0	22	117.3	91.7	25.6	86.2	117.5	-31.3	105.5	101.8	3.7
	6	109.0	116.0	-7	98.0	113	-15	119.0	95.0	24	126.7	91.5	35.2	63.6	106.8	-43.2	109.0	104.1	4.9
	7	113.0	106.0	7	101.0	100.0	1	117.0	96.0	21	120.5	72.9	47.6	52.6	89.7	-37.1	95.8	99.3	-3.5
Bottom	8	101.0	99.0	2	87.0	87.0	0	97.0	86.0	11	59.9	43.8	16.1	38.8	46.9	-8.1	65.7	77.3	-11.6

TABLE 12

SUMMARY OF THE SEQUENTIAL LONGITUDINAL STUDY
MEANS & S.E. OF 10 PATIENTS

Overall Lung Function Measurements	Control Mean of 10 patients	1 month Mean of 10 patients	3 months Mean of 9 patients	6 months Mean of 9 patients	9 months Mean of 8 patients	12 months Mean of 8 patients
TLC (litres)	5.70 ± 0.2 (111.9 ± 3.3)	5.48 ± 0.2 (107.7 ± 3.9)	5.40 ± 0.2 (104.0 ± 3.5)	5.17 ± 0.1 (99.6 ± 1.7)	5.05 ± 0.1 (97.6 ± 2.5)	5.19 ± 0.1 (100.1 ± 1.2)
VC (litres)	3.48 ± 0.2 (113.6 ± 6.1)	3.56 ± 0.2 (116.9 ± 5.2)	3.47 ± 0.2 (111.0 ± 5.3)	3.34 ± 0.2 (105.5 ± 5.4)	3.34 ± 0.2 (105.5 ± 6.3)	3.33 ± 0.2 (106.6 ± 6.2)
RV (litres)	2.22 ± 0.2 (125.9 ± 12.5)	1.97 ± 0.15 (110.4 ± 10.2)	1.94 ± 0.25 (109.6 ± 12.0)	1.83 ± 0.2 (104.9 ± 9.2)	1.75 ± 0.2 (94.2 ± 10.4)	1.86 ± 0.2 (98.5 ± 10.0)
RV/TLC (%)	39 ± 4.0 (111.3 ± 10.0)	35 ± 2.7 (102.2 ± 6.0)	36 ± 3.6 (107.3 ± 10.5)	35 ± 3.5 (105.0 ± 9.3)	34 ± 4.3 (98.9 ± 10.7)	36 ± 4.1 (104.2 ± 10.1)
FEV_1 (litres)	2.72 ± 0.2 (119.0 ± 7.3)	2.73 ± 0.2 (119.7 ± 7.6)	2.67 ± 0.2 (115.0 ± 8.5)	2.71 ± 0.25 (116.4 ± 9.4)	2.65 ± 0.3 (113.8 ± 10.5)	2.61 ± 0.3 (112.2 ± 10.5)
FVC (litres)	3.21 ± 0.3 (110.8 ± 8.5)	3.49 ± 0.2 (121.4 ± 6.9)	3.37 ± 0.25 (114.2 ± 8.5)	3.33 ± 0.3 (112.5 ± 10.0)	3.30 ± 0.25 (111.5 ± 8.4)	3.24 ± 0.3 (109.7 ± 10.0)
FEV_1/FVC (%)	85 ± 2.1 (107.4 ± 2.3)	77 ± 2.7 (94.8 ± 3.5)	79 ± 2.6 (96.2 ± 3.4)	81 ± 2.2 (101.9 ± 2.4)	79 ± 3.65 (98.3 ± 4.2)	81 ± 2.9 (99.4 ± 3.5)
$\dot{V}_{max}$ 50 (L/sec)	3.57 ± 0.40	3.55 ± 0.50	3.53 ± 0.48	3.51 ± 0.45	3.52 ± 0.52	3.59 ± 0.54
$\dot{V}_{max}$ 30 (L/sec)	1.83 ± 0.25	1.81 ± 0.28	1.85 ± 0.28	1.91 ± 0.24	1.74 ± 0.26	1.79 ± 0.32
TC_O (mmol/min/kPa)	6.60 ± 0.4 (76.7 ± 4.8)	6.52 ± 0.3 (75.9 ± 3.1)	6.72 ± 0.2 (77.6 ± 2.4)	6.95 ± 0.2 (80.7 ± 2.9)	6.61 ± 0.2 (77.2 ± 4.3)	6.76 ± 0.25 (78.9 ± 4.4)
sGaw (sec.$^{-1}$kPa^{-1})	1.24 ± 0.10	1.41 ± 0.14	1.27 ± 0.12	1.42 ± 0.15	1.48 ± 0.15	1.33 ± 0.14

TABLE 13

Perfusion/Unit Alveolus ($\dot{Q}/E$%) [average value for the upper 3 segments] of the irradiated and the non-irradiated lungs in 10 women before radiotherapy (control) and at different intervals after radiotherapy

Patient No.	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
1	69.0	68.4	0.6	47.3	75.8	-28.5	45.6	71.3	-25.7	46.3	80.2	-33.9	38.9	73.6	-34.7	61.0	72.1	-11.1
2	73.1	88.6	-15.5	56.8	74.7	-17.9	Patient Declined Further Study											
3	70.3	70.5	-0.2	47.7	62.9	-15.2	39.4	45.6	-6.2	50.8	54.6	-3.8	60.1	67.0	-6.9	74.7	74.7	0.0
4	52.1	62.1	-10.0	47.8	73.3	-25.5	54.0	56.7	-2.7	69.8	96.2	-26.4	85.2	89.2	-4.0	54.8	81.4	-26.6
* 5	111.9	120.1	-8.2	103.0	107.6	-4.6	96.5	108.0	-11.5	104.9	108.5	-3.6	Technical Error			60.9	66.7	-5.8
6	66.0	71.1	-5.1	65.9	77.1	-11.2	51.1	56.2	-5.1	47.5	48.1	-0.6	71.7	59.0	12.7	95.7	94.4	1.3
* 7	92.3	127.2	-34.9	93.3	89.7	3.6	120.0	114.4	5.6	112.2	121.9	-9.7	110.4	97.8	12.6	73.3	97.3	-24.0
8	65.4	71.0	-5.6	68.6	83.7	-15.1	53.6	71.4	-17.8	59.4	78.2	-18.8	Patient Developed Liver Metastases					
9	98.5	84.4	14.1	109.0	91.2	17.8	103.7	88.5	15.2	97.3	90.7	6.6	86.5	70.5	16.0	107.9	114.2	-6.3
10	66.0	64.1	1.9	71.0	72.3	-1.3	41.4	48.8	-7.4	63.0	76.3	-13.3	81.3	82.4	-1.1	81.6	88.7	-7.1
Mean	69.6	70.3	-0.6	65.3	76.6	-11.3	55.5	62.6	-7.1	62.0	74.9	-12.9	70.6	73.6	-3.0	79.3	87.6	-8.3
S.E.	±5.3	±2.7	±2.9	±8.3	±3.4	±5.9	±8.3	±5.7	±4.8	±6.7	±6.7	±5.5	±7.5	±4.4	±7.4	±8.3	±6.3	±4.1

*The data of these patients was excluded in calculations of the means because of malpositioning of the patient.

TABLE 14

Lung Volume (V%) [average value for the upper 3 segments] of the irradiated and the non-irradiated lungs in 10 women before radiotherapy (control) and at different intervals after radiotherapy

Patient No.	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
1	6.02	5.55	0.47	6.70	5.10	1.60	5.37	4.53	0.84	6.13	5.23	0.90	4.90	4.27	0.63	5.73	5.87	-0.14
2	6.32	5.19	1.13	4.93	5.30	-0.37	Patient Declined Further Study											
3	5.27	5.40	-0.13	6.13	7.03	-0.90	4.80	5.47	-0.67	5.67	6.37	-0.70	5.80	6.10	-0.30	5.00	4.57	0.43
4	5.37	5.23	0.14	4.73	4.93	-0.20	5.57	5.63	-0.06	5.40	5.03	0.37	4.80	5.47	-0.67	4.14	4.80	-0.66
*5	6.00	6.40	-0.40	5.33	6.10	0.40	5.60	5.83	-0.23	5.63	6.20	-0.57	Technical Error			5.50	6.63	-1.13
6	5.47	6.20	-0.73	4.80	6.43	-1.63	4.93	6.03	-1.10	5.57	5.07	0.50	4.57	4.77	-0.20	4.49	5.36	-0.87
*7	6.33	5.53	0.80	5.63	4.80	0.83	5.13	4.97	0.16	4.00	4.60	-0.60	3.83	5.10	-1.27	5.45	5.60	-0.15
8	4.60	5.37	-0.77	4.40	5.90	-1.50	4.27	5.63	-1.36	4.37	4.97	-0.60	Patient Developed Liver Metastases					
9	3.63	3.90	-0.27	4.23	4.80	-0.57	4.90	5.77	-0.87	5.01	4.96	0.05	5.50	5.53	-0.03	5.37	5.93	-0.56
10	5.67	5.73	-0.06	5.93	4.80	1.13	5.90	4.73	1.17	5.14	5.18	-0.04	5.10	6.20	-1.10	5.47	5.87	-0.40
Mean	5.15	5.34	-0.19	5.27	5.57	-0.30	5.11	5.40	-0.29	5.33	5.26	0.07	5.11	5.39	-0.28	5.03	5.40	-0.37
S.E.	±0.3	±0.3	±0.2	±0.4	±0.3	±0.5	±0.2	±0.2	±0.4	±0.2	±0.2	±0.2	±0.2	±0.3	±0.2	±0.25	±0.2	±0.2

*The data of these patients were excluded in calculations of the means because of mal-positioning of the patient.

TABLE 15

Ventilation/Unit Alveolus ($\dot{V}/E\%$) at 0.2 L/s [average value for the upper 3 segments] of the irradiated and the non-irradiated lungs in 10 women before radiotherapy (control) and at different intervals after radiotherapy

Patient No.	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
1	94.9	105.7	-10.8	76.3	114.2	-37.9	68.6	73.4	-4.8	90.2	72.9	17.3	71.1	61.4	9.7	96.1	69.2	26.9
2	95.5	100.9	-5.4	94.9	102.8	-7.9	Patient Declined Further Study											
3	58.8	64.7	-5.9	99.2	89.9	9.3	79.6	85.2	-5.6	88.9	73.0	15.9	92.3	102.4	-10.1	116.4	78.3	38.1
4	86.0	93.1	-7.1	111.7	110.3	1.4	94.2	111.2	-17.0	92.0	92.7	-0.7	95.0	95.9	-0.9	105.0	97.5	7.5
*5	111.2	165.1	-53.9	117.1	109.8	7.3	103.5	100.0	3.5	92.3	123.1	-30.8	Technical Error			82.2	84.7	-2.5
6	111.4	86.1	25.3	74.1	80.7	-6.6	90.9	92.7	-1.8	110.3	78.5	31.8	98.7	101.8	-3.1	105.8	105.8	0.0
*7	93.9	116.7	-22.8	101.5	137.9	-36.4	111.5	118.0	-6.5	127.5	136.6	-9.1	83.7	101.5	-17.8	90.9	96.2	-5.3
8	84.7	84.9	-0.2	88.0	83.4	4.6	74.5	86.4	-11.9	73.1	86.6	-13.5	Patient Developed Liver Metastases					
9	87.1	87.2	-0.1	109.5	104.3	5.2	126.2	103.1	23.1	91.6	91.5	0.1	85.9	75.7	10.2	73.6	101.4	-27.8
10	107.8	105.0	2.8	96.2	109.8	-13.6	81.8	109.1	-27.3	74.1	74.5	-0.4	71.1	81.8	-10.7	87.8	92.1	-4.3
Mean	90.1	90.0	0.06	93.6	98.9	-5.4	88.0	94.4	-6.5	88.6	81.4	7.2	85.7	86.5	-0.8	97.4	90.7	6.70
S.E.	±6.6	±5.3	±4.5	±5.6	±5.3	±6.2	±7.2	±5.3	±5.9	±4.7	±3.3	±5.7	±4.9	±6.7	±3.8	±6.2	±5.8	±9.6

*The data of these patients was excluded in calculations of the means because of malpositioning of the patient.

TABLE 16

Ventilation/Unit Alveolus ($\dot{V}/E\%$) at 1.5 L/s [average value for the upper 3 segments] of the irradiated and the non-irradiated lungs in 10 women before radiotherapy (control) and at different intervals after radiotherapy

Patient No.	Control			1 month			3 months			6 months			9 months			12 months		
	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff	Irr	Non-Irr	Diff
1	103.2	93.5	9.7	82.5	72.4	10.1	83.1	89.1	-6.0	94.1	92.8	1.3	85.4	93.3	-7.9	101.4	92.1	9.3
2	111.9	112.0	-0.1	101.5	84.0	17.5	Patient Declined Further Study											
3	88.6	85.4	3.2	97.5	105.0	-7.5	86.1	81.9	4.2	82.6	74.4	8.2	82.0	82.5	-0.5	108.9	96.5	12.4
4	93.9	106.7	-12.8	109.8	101.6	8.2	95.9	98.1	-2.2	98.6	89.9	8.7	93.9	87.3	6.6	102.7	91.3	11.4
*5	89.6	125.2	-35.6	113.9	114.6	-0.7	111.6	122.3	-10.7	112.7	133.2	-20.5	Technical Error			83.1	88.3	-5.2
6	89.9	99.5	-9.6	134.5	138.4	-3.9	91.7	76.1	15.6	107.0	77.7	29.3	107.2	101.0	6.2	110.7	107.0	3.7
*7	145.2	135.1	10.1	132.5	154.2	-21.7	161.5	131.2	30.3	120.4	132.0	-11.6	87.6	121.8	-34.2	121.1	124.0	-2.9
8	80.6	93.1	-12.5	99.8	99.9	-0.1	102.3	95.3	7.0	96.6	92.9	3.7	Patient Developed Liver Metastases					
9	97.2	117.1	-19.9	129.0	129.6	-0.6	135.4	115.4	20.0	114.0	106.7	7.3	90.2	86.2	4.0	112.9	109.9	3.0
10	84.9	91.9	-7.0	102.8	95.8	7.0	87.5	88.0	-0.5	111.5	97.0	14.5	109.8	122.9	-13.1	98.7	102.1	-3.4
Mean	91.2	98.2	-7.0	108.0	106.1	1.9	97.4	92.0	5.4	100.6	90.2	10.4	94.7	95.5	-0.78	105.9	99.8	6.07
S.E.	±2.9	±4.0	±3.8	±6.9	±8.3	±2.5	±6.8	±4.8	±3.6	±4.2	±4.2	±3.5	±4.7	±6.1	±3.3	±2.3	±3.2	±3.0

*The data of these patients was excluded in calculations of the means because of malpositioning of the patient.

TABLE 17

CLINICAL AND FUNCTIONAL MEASUREMENTS IN 23 WOMEN, WITH NO RADIOLOGICAL CHANGES, 1-14 YEARS AFTER RADIATION THERAPY FOR THEIR BREAST CANCER

Case No.	Age (years)	Smoking	Height (metres)	Weight (kilos)	Post RT (years)	Min. Rad. dose (rads)	Histopath. Diagnosis of Tumour	Stage	Side	Hb (g/dl)	WBC x10^9/L	ECG	TLC (litres)	VC (litres)	RV (litres)	RV/TLC%	FEV_1 (litres)	FVC (litres)	FEV_1/FVC%	$\dot{V}_{max}50$ (L/sec)	$\dot{V}max30$ (L/sec)	TC_O (mmol/min/kPa)	sGaw (sec.$^{-1}$kPa^{-1})	Regional Lung Function: Upper 3 Irr-Upper 3 Non-Irr $\dot{V}$ %	$\dot{Q}$/E %	$\dot{V}$/E %
1	51	S	1.63	58.5	12	4150	Scirrhous	I	R	14.1	9.2	N	4.91 (101)	3.65 (126)	1.26 (70)	26 (74)	2.85 (134)	3.65 (140)	78 (99)	4.19	2.07	5.36 (63)	1.343	1.40	-50.5	+1.8
2	72	NS	1.56	64.0	6	3940	Scirrhous	I	R	14.5	6.2	N	4.24 (101)	2.76 (123)	1.48 (80)	35 (86)	2.00 (121)	2.55 (121)	78 (107)	3.65	1.60	6.32 (80)	1.278	-0.13	+7.4	23.9
3	61	S	1.63	65.5	3	4130	Scirrhous	II	L	15.5	10.0	T↓	4.47 (98)	2.76 (106)	1.71 (93)	38 (100)	2.00 (108)	2.70 (118)	74 (97)	2.67	1.33	7.61 (94)	1.560	1.07	-31.5	2.9
4	44	NS	1.67	49.5	2	4180	Infiltrating	I	L	12.9	5.3	T↓	4.70 (90)	2.91 (92)	1.79 (97)	38 (114)	2.60 (109)	3.10 (106)	84 (104)	4.88	2.66	6.57 (76)	1.815	-0.70	-14.8	12.9
5	50	NS	1.56	71.5	2	4035	Intraduct	II	R	12.6	5.7	N	4.24 (98)	3.20 (124)	1.04 (68)	25 (71)	2.60 (124)	3.05 (120)	86 (108)	5.91	3.71	6.70 (80)	2.047	0.47	-1.8	4.6
6	55	S	1.64	56.7	2	4140	Intraduct	I	R	14.5	4.1	N	5.31 (110)	3.45 (123)	1.86 (101)	35 (97)	2.20 (105)	3.20 (123)	69 (89)	1.96	1.02	5.11 (60)	1.293	-0.27	-7.8	0.1
7	59	S	1.61	86.9	14	4320	Infiltrating	II	R	14.8	6.1	N	7.00 (154)	3.30 (127)	3.70 (208)	53 (143)	1.40 (74)	3.20 (138)	44 (77)	0.93	0.37	4.67 (57)	0.543	0.30	-5.7	13.5
8	58	S	1.57	52.0	13	4000	Infiltrating	I	L	15.0	5.5	N	3.45 (81)	2.17 (88)	1.28 (78)	37 (100)	1.75 (95)	2.05 (92)	85 (110)	2.79	1.46	7.16 (90)	1.505	-0.17	-20.6	-24.6
9	52	S	1.62	76.0	5	4100	Infiltrating	II	R	9.8	6.6	N	6.11 (130)	3.53 (127)	2.58 (147)	42 (117)	2.70 (123)	3.55 (130)	76 (96)	3.82	1.82	5.52 (63)	1.197	0.03	-31.6	5.6
10	65	XS	1.55	60.2	7	3930	Intraduct	III	R	14.4	6.3	N	4.16 (104)	2.73 (122)	1.43 (87)	34 (87)	1.70 (101)	2.60 (126)	65 (87)	3.60	1.93	7.78 (134)	1.315	1.10	-12.8	-19.2
11	73	S	1.60	59.5	5	4110	Scirrhous	II	L	14.2	6.9	T↓	3.81 (90)	2.22 (98)	1.59 (85)	42 (102)	1.30 (90)	2.10 (118)	62 (85)	2.00	1.31	4.61 (60)	1.139	-0.03	-17.4	3.0
12	52	S	1.58	56.8	4	4039	Intraduct	I	R	12.1	4.0	N	5.80 (131)	3.10 (117)	2.70 (167)	47 (131)	2.70 (126)	3.20 (121)	84 (108)	3.91	2.07	5.26 (61)	1.011	-0.50	-9.8	3.5
13	51	NS	1.62	60.5	6	4000	Adeno	I	L	14.0	5.6	N	4.23 (89)	2.80 (100)	1.43 (82)	34 (97)	1.95 (95)	2.65 (107)	74 (94)	2.92	1.08	6.32 (76)	2.116	-0.93	+10.9	7.3
14	50	NS	1.58	100.5	6	3930	Adeno	III	L	13.1	5.6	T↓	4.17 (94)	3.03 (114)	1.14 (71)	27 (77)	2.65 (125)	2.90 (112)	91 (115)	6.36	2.80	6.40 (75)	1.572	-0.63	-1.1	25.2
15	67	XS	1.52	64.0	9	4150	Intraduct	I	R	13.5	5.2	N	3.43 (92)	2.17 (105)	1.26 (80)	37 (94)	1.60 (103)	2.15 (114)	74 (99)	4.05	1.91	4.79 (64)	2.149	1.03	-6.4	-6.8
16	58	NS	1.57	50.0	8	3760	Scirrhous	III	R	14.5	6.2	N	4.00 (94)	2.70 (110)	1.30 (79)	33 (89)	2.25 (122)	2.70 (120)	83 (108)	3.33	2.07	6.39 (79)	1.134	0.90	-7.1	-7.5
17	45	S	1.52	48.0	5	4075	Intraduct	I	R	14.5	7.4	N	4.36 (106)	3.80 (116)	0.56 (41)	13 (39)	2.90 (144)	3.60 (155)	81 (100)	5.45	2.63	6.68 (85)	1.986	0.53	-3.8	6.6
18	53	S	1.53	49.0	11	4340	Anaplastic	II	L	13.5	8.6	T↓	4.46 (78)	3.30 (71)	1.16 (79)	26 (73)	2.45 (133)	3.20 (148)	77 (98)	4.57	1.84	6.19 (80)	1.590	-0.70	-21.5	4.34
19	73	NS	1.53	49.5	3	4176	Squamous	III	R	13.7	7.2	N	2.90 (78)	2.10 (106)	0.80 (49)	28 (68)	1.50 (104)	1.95 (110)	77 (103)	3.58	2.11	5.22 (70)	1.420	0.67	+0.12	-8.8
20	67	NS	1.70	60.5	11	4160	Scirrhous	II	R	15.0	8.0	N	4.13 (82)	2.43 (87)	1.70 (79)	41 (104)	1.90 (100)	2.25 (92)	84 (113)	2.88	1.88	5.13 (60)	1.911	-0.50	-3.0	-6.15
21	61	S	1.57	49.0	1	4074	Infiltrating	II	R	15.3	5.8	N	5.04 (119)	2.61 (107)	2.43 (146)	48 (127)	1.80 (101)	2.60 (118)	69 (91)	1.45	0.64	4.22 (53)	0.889	0.76	-47.5	-18.8
22	42	NS	1.74	92.7	0	4000	Scirrhous	I	L	10.8	4.4	T↓	4.76 (83)	3.75 (107)	1.01 (49)	21 (64)	3.00 (116)	3.55 (110)	85 (105)	4.71	2.39	7.43 (101)	1.847	-0.03	-11.8	10.2
23	54	NS	1.70	64.0	1	4114	Anaplastic	III	L	13.7	5.0	T↓	5.22 (103)	3.08 (103)	2.14 (112)	41 (117)	2.00 (91)	2.95 (78)	68 (87)	2.34	1.11	6.67 (76)	1.384	-0.86	-14.4	9.8
Mean	57		1.60	62.8									4.56 (100)	2.94 (109)	1.62 (93)	35 (94)	2.17 (111)	2.85 (118)	76 (99)	3.56	1.82	6.01 (76)	1.480	0.12	-13.1	1.9
S.E.	±1.9		±0.01	±2.99									±0.19	±0.11	±0.15	±1.93	±0.11	±0.11	±2.12	±0.29	±0.16	±0.21	±0.09	±0.15	±3.2	±2.6

TABLE 18

CLINICAL AND FUNCTIONAL MEASUREMENTS IN 25 WOMEN, WITH RADIOLOGICAL CHANGES, 1-14 YEARS AFTER RADIATION THERAPY FOR THEIR BREAST CANCER

Case No.	Age (years)	Smoking	Height (metres)	Weight (kilos)	Post RT (years)	Min. Rad. dose (rads)	Histopath. Diagnosis of Tumour	Stage	Side	Hb (g/dl)	WBC x10^9/L	ECG	CXR	TLC (litres)	VC (litres)	RV (litres)	RV/TLC%	FEV_1 (litres)	FVC (litres)	FEV_1/FVC%	$\dot{V}_{max}50$ (L/sec)	$\dot{V}_{max}30$ (L/sec)	TCO (mmol/min/kPa)	sGaw ($sec.^{-1}kPa^{-1}$)	Regional Lung Function: Upper 3 Irr-Upper 3 Non-Irr $\dot{V}$ %	$\dot{Q}/\dot{E}$ %	$\dot{V}/\dot{E}$ %
1	49	NS	1.63	58.0	2	4183	Invasive	II	L	12.7	4.4	N	+	5.55 (113)	3.08 (105)	1.47 (82)	27 (74)	2.60 (120)	3.10 (118)	84 (106)	4.47	1.90	5.97 (69)	2.041	-0.90	-5.6	0.3
2	47	S	1.63	54.0	5	4075	Anaplastic	I	R	15.5	7.3	N	+++	4.51 (93)	2.46 (84)	2.05 (118)	46 (135)	1.45 (66)	2.25 (84)	64 (80)	1.26	0.70	6.37 (74)	0.557	-0.32	-67.1	-15.2
3	57	XS	1.58	70.8	11	4000	Intraduct	I	R	13.3	4.5	N	+	4.31 (99)	3.28 (130)	1.03 (62)	24 (65)	2.50 (100)	2.90 (92)	86 (111)	4.11	1.89	7.52 (92)	1.754	-0.24	-24.9	-5.6
4	46	NS	1.55	59.3	4	4035	Intraduct	I	R	14.1	6.5	N	+	4.56 (106)	3.30 (126)	1.26 (86)	28 (83)	2.60 (126)	3.30 (138)	79 (99)	3.18	2.27	8.02 (100)	1.497	-0.56	45.1	3.2
5	42	S	1.62	69.2	3	4060	Anaplastic	I	R	13.1	9.6	N	+++	4.49 (92)	3.40 (99)	1.09 (66)	24 (73)	2.65 (116)	3.40 (124)	78 (96)	3.77	2.05	5.77 (66)	1.612	0.27	-34.0	15.9
6	54	NS	1.58	58.9	5	4100	Anaplastic	II	L	13.6	5.2	N	+	4.90 (111)	3.38 (131)	1.52 (93)	31 (86)	2.85 (148)	3.55 (153)	80 (103)	4.52	2.63	6.64 (81)	1.413	-0.38	2.1	1.1
7	39	S	1.63	65.4	4	4080	Intraduct	I	L	13.9	6.3	T ↓	+	4.69 (98)	3.10 (100)	1.59 (95)	34 (106)	2.50 (106)	3.25 (115)	77 (94)	3.66	1.79	6.86 (77)	1.643	-0.39	-6.9	3.37
8	61	S	1.77	67.0	12	4180	Anaplastic	I	L	14.0	4.7	N	+	5.77 (102)	4.10 (127)	1.67 (137)	29 (77)	2.95 (130)	4.15 (140)	71 (93)	3.28	1.45	6.30 (67)	0.900	0.01	-21.2	24.4
9	54	XS	1.62	55.0	6	3840	Anaplastic	I	R	14.6	5.9	N	+	5.29 (113)	3.45 (126)	1.84 (104)	35 (97)	2.45 (120)	3.20 (128)	77 (99)	2.70	1.34	5.98 (71)	1.087	-0.03	6.7	0.8
10	52	S	1.61	76.7	12	4200	Scirrhous	I	R	13.2	8.0	N	+	4.59 (99)	3.05 (111)	1.54 (99)	34 (96)	2.45 (113)	3.00 (108)	82 (104)	3.93	2.55	6.56 (76)	1.176	0.68	-7.9	-7.9
11	55	S	1.70	60.0	12	4260	Anaplastic	III	L	13.0	5.5	N	+	4.05 (77)	2.60 (85)	1.45 (71)	36 (99)	2.15 (98)	2.70 (97)	80 (102)	2.55	1.45	7.01 (79)	1.311	-0.71	-10.0	4.4
12	48	NS	1.55	52.0	4	4153	Scirrhous	I	L	12.1	5.4	N	+	4.43 (104)	3.10 (120)	1.33 (89)	30 (87)	2.20 (110)	3.05 (130)	72 (91)	3.13	1.64	6.68 (83)	1.616	0.52	-6.9	1.8
13	73	S	1.66	65.5	13	4000	Scirrhous	I	R	15.3	6.7	N	+	5.43 (116)	2.68 (106)	2.75 (133)	51 (124)	1.40 (79)	2.35 (100)	60 (82)	1.60	0.88	6.42 (76)	0.784	1.02	-7.6	-6.7
14	75	NS	1.61	83.5	10	4060	Papillary	I	R	14.7	7.5	N	+	3.71 (87)	2.30 (101)	1.41 (73)	38 (91)	1.60 (99)	1.90 (90)	84 (116)	3.39	1.45	6.43 (80)	1.488	-0.06	11.9	14.6
15	43	S	1.63	79.1	1	4025	Squamous cell	III	R	12.9	9.9	N	+++	4.20 (85)	3.05 (101)	1.15 (68)	27 (82)	2.80 (123)	3.35 (123)	84 (104)	4.00	2.96	5.10 (60)	1.629	0.93	-0.5	4.8
16	62	NS	1.60	54.0	1	4095	Infiltrating	I	L	14.0	4.9	N	++	4.23 (96)	3.13 (125)	1.10 (62)	26 (68)	2.15 (118)	2.80 (123)	77 (101)	2.07	0.89	5.41 (67)	1.623	-0.18	-7.3	28.8
17	63	NS	1.55	65.0	6	3930	Scirrhous	III	L	12.5	7.0	T ↓	+	4.09 (102)	2.55 (112)	1.54 (95)	38 (99)	2.00 (114)	2.40 (111)	83 (110)	2.98	1.73	6.35 (81)	1.030	-0.85	-7.3	-0.5
18	50	S	1.60	63.5	11	4200	Anaplastic	I	R	13.2	5.7	N	+	5.54 (120)	3.20 (116)	2.34 (140)	42 (120)	2.40 (116)	3.15 (126)	76 (96)	2.88	1.30	6.61 (80)	1.325	0.08	-11.6	4.6
19	52	S	1.50	70.5	7	3930	Intraduct	I	L	14.1	4.3	T ↓	+	3.73 (97)	2.85 (125)	0.88 (60)	24 (68)	2.40 (122)	2.90 (122)	83 (106)	4.17	2.38	5.24 (68)	2.478	-0.83	-26.2	10.7
20	69	NS	1.55	52.0	10	4060	Adeno	I	R	14.2	6.7	N	+	3.30 (84)	2.10 (98)	1.20 (71)	36 (90)	1.40 (89)	2.25 (118)	62 (84)	2.27	0.95	5.21 (68)	1.297	1.10	-3.0	-12.2
21	58	S	1.61	50.9	9	4050	Anaplastic	I	R	13.1	5.3	N	+	4.46 (98)	3.65 (139)	0.81 (46)	18 (49)	2.05 (111)	3.95 (176)	52 (68)	1.74	1.15	4.08 (50)	1.540	1.87	-33.7	-21.0
22	64	S	1.60	49.5	3	4130	Infiltrating	II	R	13.7	7.2	N	++	3.48 (80)	2.60 (106)	0.88 (49)	25 (65)	2.20 (127)	2.90 (136)	76 (101)	3.47	2.35	3.95 (49)	2.214	0.20	-22.0	3.6
23	60	NS	1.70	65.0	8	3950	Scirrhous	II	R	14.6	6.0	N	++	4.99 (96)	3.63 (123)	1.36 (65)	27 (72)	2.45 (117)	3.50 (130)	70 (92)	3.07	0.66	9.30 (105)	1.870	0.70	-16.1	-6.4
24	36	NS	1.59	49.0	0	4135	Intraduct	II	L	13.2	6.4	T ↓	+	4.61 (97)	3.40 (100)	1.21 (88)	26 (84)	3.20 (135)	3.50 (126)	91 (110)	3.95	2.22	7.35 (87)	1.703	-1.10	3.22	-10.7
25	57	XS	1.60	85.4	1	3910	Invasive	III	R	13.8	7.0	N	+	5.22 (100)	2.08 (69)	3.14 (153)	60 (163)	1.05 (50)	1.55 (58)	68 (85)	1.33	0.54	6.17 (68)	0.540	0.15	-44.4	-4.9
Mean	55		1.61	63.2										4.57 (99)	3.02 (111)	1.50 (88)	33 (90)	2.26 (110)	2.97 (119)	76 (97)	3.10	1.64	6.29 (75)	1.445	0.04	-11.8	1.25
S.E.	±2.0		±0.01	±2.09										±0.13	±0.10	±0.11	±1.90	±0.11	0.12	±1.83	±0.19	±0.13	±0.23	±0.09	±0.15	±4.2	±2.3

APPENDIX I

Effect of radiotherapy on total and regional lung function.

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When modern high voltage radiotherapy is used in combination with simple mastectomy for treatment of carcinoma of the breast, the lung apex on the treated side receives up to 4250 rads. Minor changes in overall lung function following such therapy have been reported (Emirgil and Heinemann, 1961, Journal of Applied Physiology, 16, 331), but these are more pronounced when symptomatic radiation pneumonitis develops, which occurs in about 10% of such patients (Gross, 1977, Annals of Internal Medicine, 86, 81). We have measured FEV_1, FVC, lung volumes, transfer factor, flow volume curves and airways resistance in ten women aged 35-61 years, after simple mastectomy, but before radiotherapy, and at 1, 3, 6, 9 and 12 months following 4250 rads to the axilla and supraclavicular region and 4500 to the chest wall by tangential fields given in 10 fractions over 4 weeks, as part of their treatment of carcinoma of the breast. Regional ventilation and perfusion was measured with radioactive ^{133}Xe, using a gamma camera linked on-line to a computer. Before radiotherapy, but after simple mastectomy, the mean FEV_1 was 118 (SE 7.4)% of predicted normal, FVC 111 (SE 8.5)%, TLC 112 (SE 3.3)%, RV 120 (SE 12.4)% and T_{CO} 77 (SE 4.8)% of predicted normal values. Three months after radiotherapy there was a 10%

reduction in TLC, and 28% reduction in RV, but transfer factor and the other measurements were unchanged, as were the chest x-rays. Comparison of regional ventilation between the irradiated lung and non-irradiated "control" lung, at the same vertical height, showed no changes either before radiotherapy or sequentially at 1, 3, 6, 9 and 12 months thereafter. However, there was a consistent and significant reduction in perfusion of the upper zones of the irradiated lung, corresponding to the region receiving the radiotherapy. These perfusion changes were detected in some patients as early as 1 month after radiotherapy, and returned towards normal at 9 months, but there were no radiological changes. We conclude that these doses of radiation affect the pulmonary vascular bed, in irradiated areas, even where this is not clinically or radiologically apparent. We could detect no effects of the radiation on the airways or parenchyma of the irradiated zones.

APPENDIX II

The relative distribution of airflow resistance in normal subjects and patients with airway obstruction.
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The site of airway obstruction in patients with chronic airways obstruction is probably in airways less than 2-3 mm in diameter. Some patients with asthma may show a similar pattern, but in others narrowed larger airways may be responsible for the increased resistance.

Despas, Leroux and Macklem (1972, Journal of Clinical Investiation, 51, 3235) measured changes in maximum expiratory flow (MEFV) breathing air and when breathing a 80% helium, 20% oxygen mixture (He/O_2). Maximum flow at 50% VC ($\dot{V}_{max}$ 50) breathing He/O2 was variably increased in patients with asthma, but unchanged in patients with chronic bronchitis.

We have studied normal subjects (age range 18-37 years, mean FEV_1 3.91 litres, mean FVC 4.66 litres), patients with asthma (age range 14-38 years, mean FEV_1 2.25 litres, mean FVC 3.69 litres) and patients with chronic irreversible airways obstruction (age range 55-72 years, mean FEV_1 1.65 litres, mean FVC 2.43 litres).

We have measured MEFV and specific conductance (sGaw) in a body plethysmograph breathing air and breathing He/O_2. The response to breathing He/O_2 did not distinguish the three groups using the fractional increase in $\dot{V}_{max}$ 50 compared to the $\dot{V}_{max}$ 50 breathing air. However, we found that the lower the initial $\dot{V}_{max}$ 50, the smaller the fractional increase.

At $\dot{V}_{max}$ 25 some subjects showed a reduction in maximum flow rate breathing He/O_2.

In all subjects sGaw increased on breathing He/O_2, but this increase was not related to the initial value of airway resistance (AWR). It appeared that some patients with chronic airways obstruction had a lesser response than normal subjects. Patients with asthma could not be distinguished from normal subjects.

The change in sGaw breathing He/O_2 should be more influenced by the site of airways obstruction than the $\dot{V}_{max}$ 50 as sGaw is measured at the same flow rate in all subjects. During the measurement of AWR the mean velocity of flow in the large airways is similar in all subjects and any changes in AWR with He/O_2 must arise from differences in the distribution of resistance to airflow. However, for $\dot{V}_{max}$ 50 the initial value varied, hence the mechanics of air flow in the airways in different individuals was not comparable.

The poor response of sGaw to He/O_2 in patients with chronic airways obstruction suggests that the resistance of the peripheral airways is relatively greater than normal. The distribution of resistance in our patients with asthma is normal.